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Page 1726 *for* "3:4:5:6-Dibenzyl*cyclo*hepta-3:5-diene" *read* "3:4:5:6-Dibenz*cyclo*hepta-3:5-diene".
Page 1726 *for* "3:4:5:6-Dibenzyl*cyclo*hepta-1:3:5-triene" *read* "3:4:5:6-Dibenz*cyclo*hepta-1:3:5-triene".

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Page 176, line 4 of Summary; page 177, lines 15 and 25 of text, *for* "·CO·[CH:CH]$_n$·CO·" *read* "·CO·[C:C]$_n$·CO·".

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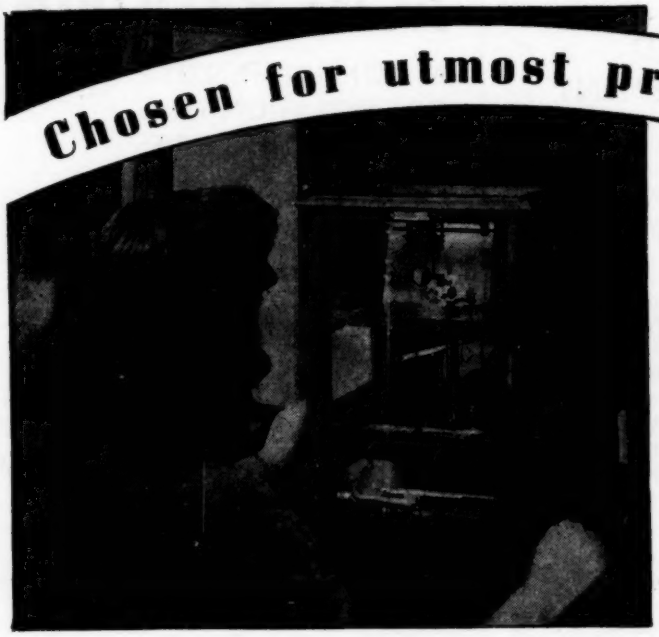

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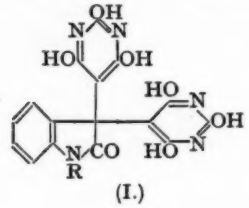
112. *The Condensation of Isatin and of* 1-*Methylisatin with Barbituric Acid.*

By F. E. KING. T. J. KING, and G. B. THOMPSON.

Isatin and barbituric acid react under aqueous acid conditions giving 3 : 3-*di*-(5-*barbituryl*)-*oxindole* (I, R = H), which is transformed by methanolic hydrogen chloride into *methyl* 2 : 4-*dihydroxy*-1 : 3-*diaza-acridine*-5-*carboxylate* (II, R = CO_2Me). Similar products, *i.e.*, (I, R = Me) and (VI, R = Me), can be prepared from 1-methylisatin. Hydrolysis of (II, R = CO_2Me) gave the corresponding *acid* (II, R = CO_2H) which was degraded to known 2-hydroxyquinolinecarboxylic acids. From the *acid chloride* the *amide* (II, R = $CO{\cdot}NH_2$) was obtained, and this was converted into 5-*amino*-2 : 4-*dihydroxy*-1 : 3-*diaza-acridine hydrochloride*.

BECAUSE the heterocyclic system which they contain has several features in common with that of the *iso*alloxazines, a number of diaza-acridines were recently prepared as potential riboflavin antagonists (see F. E. and T. J. King, *J.*, 1947, 726). They were obtained by the action of *o*-aminobenzaldehyde on pyrimidines with tautomerisable groups in the 2 : 4 : 6-positions, a method of considerable flexibility, though limited in its application to *benz*-substituted diaza-acridines by the general inaccessibility of the necessary *o*-aminobenzaldehydes. With the idea of overcoming this disadvantage by using derivatives of isatin in place of the aminobenzaldehyde components—as in the Pfitzinger modification of Friedländer's quinoline synthesis—the condensation of isatin with barbituric acid as a typical pyrimidine was investigated. The carboxylic acids resulting from such condensations have a further interest in that they might be used in the preparation of the unknown 5-amino-1 : 3-diaza-acridines, analogues of the biologically active 5-aminoacridines.



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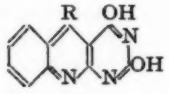

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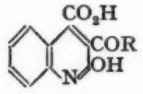

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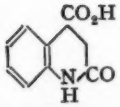

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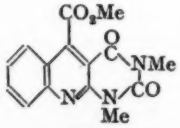

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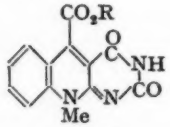

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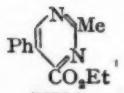

(VII.)

From experience with *o*-aminobenzaldehyde in its reaction with the aminohydroxypyrimidines (F. E. and T. J. King, *loc. cit.*), isatin was not expected to condense with barbituric acid under the alkaline conditions of the normal Pfitzinger synthesis, and this was confirmed by experiment. Neither did any condensation occur in boiling water, but on addition of hydrochloric acid a colourless solid separated, which from analysis was evidently 3 : 3-*di*-(5-*barbituryl*)*oxindole* (I, R = H). In this respect, therefore, the pyrimidine behaves as a derivative of malonic acid, of which both the ethyl ester and dinitrile give similar di-substituted oxindoles (Zrike and Lindwall, *J. Amer. Chem. Soc.*, 1936, **58**, 49; Walter, *Ber.*, 1902, **35**, 1321).

The dibarbituryloxindole was decomposed by alkalis, and underwent hydrolysis into its components even on being heated with water, as was evident from the colour of the solution and from the isolation of isatin and barbituric acid in the form of derivatives. Conditions appropriate to the transformation of the dimalonyloxindoles to quinolines could not, therefore, be applied to the conversion of (I) into the required tricyclic system (II), and acid hydrolysis was therefore attempted. Heating with methanolic hydrogen chloride led (apparently by elimination of a barbituric acid residue) to the formation of a colourless *methyl* ester, and to this the constitution (II, R = CO_2Me) was assigned, since a barbiturylindogenide, the only likely alternative, would undoubtedly be coloured.

Apart from hydrolysis of the ester group, giving 2 : 4-*dihydroxy*-1 : 3-*diaza-acridine*-5-*carboxylic acid* (II, R = CO_2H), the new product was stable to boiling aqueous alkali, but at higher temperatures under pressure degradation to the 2-*hydroxy*-4-*carboxyquinoline*-3-*carboxy-amide* (III, R = NH_2) occurred. It is of interest to note that 2 : 4-dihydroxy-1 : 3-diaza-acridine

(II, R = H) is hydrolysed by alkali under pressure to 2-hydroxyquinoline-3-carboxylic acid (Conrad and Reinbach, *Ber.*, 1901, **34**, 1339), although the precise experimental conditions are not recorded.

From the amido-acid (III, R = NH_2) a *monomethyl* ester was obtained, and, by treatment in 40% sulphuric acid solution with sodium nitrite, the corresponding dicarboxylic acid (III, R = OH). This had already been prepared from 3 : 3-dimalonyloxindole (Zrike and Lindwall, *loc. cit.*), but, its melting point being outside the usual range, identification was uncertain. It was therefore reduced by zinc in acetic acid, as described by Zrike and Lindwall (*loc. cit.*); loss of the 3-carboxyl group then occurred, leading to the more easily identified 2-keto-tetrahydroquinoline-4-carboxylic acid (IV).

It was later found that the action of hot concentrated hydrochloric acid on the dibarbituryl-oxindole was an alternative method for the preparation of (II, R = CO_2H). Identity of the products from the two sources was established by their hydrolysis to the same amidoquinoline-carboxylic acid (III, R = NH_2), and from further evidence cited later.

Decarboxylation of the diaza-acridine (II, R = CO_2H) was attempted by heating with copper chromite in quinoline, but even in boiling solutions the acid remained unchanged. The inactivity of the carboxyl group in this derivative was also apparent from unsuccessful experiments on its re-esterification with methyl alcohol. By the action of boiling thionyl chloride, however, an *acid chloride* (II, R = COCl) was obtained which reacted with methanol to give the known methyl ester, and with ethanol to give its *ethyl* analogue (II, R = CO_2Et). When left in contact with ethereal diazomethane, both acid and methyl ester gave *methyl* 2 : 4-*diketo*-1 : 3-*dimethyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 3-*diaza-acridine*-5-*carboxylate* (V), the formation of this compound, one of the few in this series with an easily ascertainable melting point, both from the ester (II, R = CO_2Me) and from the acid prepared by acid hydrolysis of (I), affording definite proof of their identity. From the acid chloride and aqueous ammonia, the 5-*carboxyamide* (II, R = CO·NH_2) was prepared, and the action of sodium hypobromite on this gave 5-amino-2 : 4-dihydroxy-1 : 3-diaza-acridine, isolated as *hydrochloride*. Hydrazoic acid under the usual conditions of the Schmidt process was without action on the diaza-acridine-5-carboxylic acid.

The investigation was concluded with some experiments on the condensation of barbituric acid with 1-methylisatin. Under acid conditions, the 3 : 3-*di*-(5-*barbituryl*)-1-*methyloxindole* (I, R = Me) was formed. With methanolic hydrogen chloride rearrangement occurred as in the case of (I, R = H), the resulting *methyl* ester (VI, R = Me) bearing the same relationship to the 1 : 3-diaza-acridines as do the *iso*alloxazines to the analogous alloxazines. As was expected, the new nucleus was markedly more chromophoric, the 10-methyldiaza-acridines being brilliant yellow. The hydrolysis of (VI, R = Me) with alkali gave a carboxylic *acid* which was indistinguishable from the product obtained from the action of concentrated hydrochloric acid on the dibarbituryl-1-methyloxindole.

An alternative synthesis of 5-hydroxy- or 5-amino-diaza-acridines was at one time considered, based on the preparation of suitable pyrimidines from *o*-nitrobenzoylmalonic esters, etc., followed by reduction of the nitro-group and ring-closure, but it was not completed. In connexion with preliminary experiments, using benzoyl compounds, an improved preparation of ethyl benzoylmalonate was devised, in the course of which *ethyl dibenzoylmalonate* was isolated. The oxidation of 5-benzylbarbituric acid as a possible source of the 5-benzoylpyrimidine led, with chromic acid as reagent, to the formation of 5-*benzyldialuric acid*. The action of acetamidine on ethyl ethoxymethylenebenzoylacetate did not give 4-hydroxy-5-benzoyl-2-methylpyrimidine but the 4-*carbethoxy*-5-*phenyl* derivative (VII).

Experimental.

3 : 3-*Di*-(5-*barbituryl*)*oxindole* (I, R = H).—A suspension of isatin (14·7 g., 1 mol.) and barbituric acid (25·6 g., 2 mol.) in hot water (50 c.c.) was treated with concentrated hydrochloric acid (10 c.c.) and the mixture shaken and heated to boiling for a few minutes. The product collected after cooling was well washed with alcohol and finally with ether, which left a pale cream granular powder (27 g., 67%). This was so sparingly soluble in the usual solvents that it was recrystallised by dissolving in cold sodium hydrogen carbonate solution, from which, on the addition of dilute hydrochloric acid, 3 : 3-*di*-(5-*barbituryl*)*oxindole* separated as a monohydrate in colourless microscopic rhombohedra, m. p. 270° (decomp.) (Found : C, 47·6; H, 3·3; N, 17·7. $C_{14}H_{11}O_7N_4.H_2O$ requires C, 47·5; H, 3·2; N, 17·4%). Its decomposition on dissolving in boiling water was apparent from the red colour of the solution, and from the formation on treatment with hydroxylamine of long yellow needles of isatin-β-oxime, m. p. and mixed m. p. 218—219°. Addition of benzaldehyde to a warm aqueous solution gave a colourless solid, m. p. after crystallisation from acetic acid, 258—259° alone or mixed with 5-benzylidene-barbituric acid.

Methyl 2 : 4-*Dihydroxy*-1 : 3-*diaza-acridine*-5-*carboxylate* (II, R = CO_2Me).—The dibarbituryloxindole (7·5 g.) was suspended in methanol (70 c.c.) previously saturated with hydrogen chloride and the

mixture heated under reflux for 3 hours. After cooling, the white solid was collected and the *ester* separated from any remaining dibarbituryloxindole, etc., either by washing with dilute sodium hydrogen carbonate solution or by heating with water. The purified product (3·8 g., 70%) crystallised from a large volume of acetic acid in colourless microscopic elongated rectangular plates, m. p. >320° (Found after drying at 100° in a vacuum: C, 57·3; H, 3·5; N, 15·5. $C_{13}H_8O_4N_2$ requires C, 57·6; H, 3·3; N, 15·5%). Its solution in acetic acid fluoresces bright green in ultra-violet light. The ester is also slightly soluble in dioxan and 2-ethoxyethanol, the solutions exhibiting a brilliant blue fluorescence. It does not dissolve in cold aqueous sodium carbonate, but with dilute sodium hydroxide a yellow solution with a green fluorescence is formed. From more concentrated solutions a *sodium* salt separates as the sesquihydrate in bright yellow fine needles, m. p. >310° (Found: C, 49·0; H, 3·4; N, 12·9. $C_{13}H_8O_4N_2Na,1\frac{1}{2}H_2O$ requires C, 48·75; H, 3·4; N, 13·1%).

2 : 4-*Dihydroxy*-1 : 3-*diaza-acridine*-5-*carboxylic Acid* (II, R = CO_2H).—(*a*) The diaza-acridine methyl ester (5 g.) was heated under reflux for 20—30 minutes with 2N-sodium hydroxide (50 c.c.). When the bright yellow solution was cooled, a pale yellow sodium salt crystallised which on treatment with hydrochloric acid gave a buff-coloured solid. It was purified by dissolving in warm dilute sodium hydrogen carbonate solution (charcoal) and reprecipitating with hydrochloric acid. The resulting 2 : 4-*dihydroxy*-1 : 3-*diaza-acridine*-5-*carboxylic acid* was collected, and washed with water, alcohol, and ether (yield 4·4%). It is sparingly soluble in the ordinary organic solvents and was recrystallised from a large volume of acetic acid, from which it separated in colourless, microscopic, long, thin, rectangular prisms, m. p. >325° (Found: C, 52·5; H, 3·5; N, 15·4. $C_{12}H_7O_4N_3,H_2O$ requires C, 52·3; H, 3·3; N, 15·3%. Found in a specimen dried in a vacuum at 100°: C, 54·0; H, 3·4; N, 15·3; loss 2·9. $C_{12}H_7O_4N_3,\frac{1}{2}H_2O$ requires C, 54·1; H, 3·0; N, 15·8; loss 3·3%).

(*b*) 3 : 3-Di-(5-barbituryl)oxindole (15 g.) was heated with concentrated hydrochloric acid (75 c.c.) in an open flask on a steam-bath until most of the liquid had evaporated (*ca.* 3 hours). Water (50 c.c.) was added to the light brown residue which then turned reddish. The rose-pink solid (8·5 g.) was collected, and washed with water, alcohol, and ether. It was purified by precipitation with acid from a solution in sodium hydrogen carbonate and by crystallisation from acetic acid (Found: C, 52·5; H, 3·6. Found in a dried specimen: C, 54·5; H, 3·2; loss 3·7%).

The colourless recrystallised acid exactly resembled in form, and in the fluorescence of its solutions in the ultra-violet—which were green-yellow in acetic acid, bright blue in sodium hydrogen carbonate, intense green in sodium hydroxide, and bright blue in ethanol—the acid obtained from the methyl ester (II, R = CO_2Me). Unless several times recrystallised, however, the latter exhibited a bright yellow colour in concentrated sulphuric acid, which was also observed if the specimen derived directly from the dibarbituryloxindole by means of hydrochloric acid was treated with boiling 2N-sodium hydroxide. Both samples of recrystallised acid gave only a pale straw-yellow colour when dissolved in concentrated sulphuric acid. After being left for 2 days in a vacuum over sodium hydroxide both dissolved quite readily in warm acetic acid, but the products which very shortly afterwards separated then required the usual large volume of boiling acid for complete solution.

Methyl 2 : 4-*Diketo*-1 : 3-*dimethyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 3-*diaza-acridine*-5-*carboxylate*, (V).—A finely powdered specimen (1 g.) of 2 : 4-dihydroxy-1 : 3-diaza-acridine-5-carboxylic acid, dried at 120°, was treated with a solution of diazomethane (0·8 g.) in ether. Nitrogen was evolved as the suspension stood at room temperature, and after 24 hours the pale yellow solid (0·6 g.) was collected. The product, which was insoluble in sodium carbonate solution, was crystallised from methanol or aqueous acetic acid; the methylated *ester* was thus obtained as minute colourless needles, m. p. 220° (Found in specimen dried at 100° in a high vacuum: C, 60·0; H, 4·7; N, 14·0; OMe, 10·9. $C_{15}H_{13}O_4N_3$ requires C, 60·2; H, 4·3; N, 14·0; OMe, 10·4%).

2-*Hydroxy*-4-*carboxyquinoline*-3-*carboxyamide* (III, R = NH_2).—2 : 4-Dihydroxy-1 : 3-diaza-acridine-5-carboxylic acid (2 g.) was heated with aqueous sodium hydroxide (6 c.c. of 20%) at 180° for 5 hours. The solution was diluted with water to dissolve the product, filtered, and treated with hydrochloric acid. The colourless product (1·5 g.) being very sparingly soluble in organic solvents, it was purified by precipitation with acid from its solution in sodium hydrogen carbonate, the 2-*hydroxy*-4-*carboxyquinoline*-3-*carboxyamide* forming microscopic short prisms, m. p. 245° (decomp.) after discolouration at *ca.* 200° (Found, after dying in a vacuum at 100°: C, 56·5; H, 3·7; N, 11·9. $C_{11}H_8O_4N_2$ requires C, 56·9; H, 3·4; N, 12·1%).

Ethyl 2-*Hydroxy*-3-*carboxyamidoquinoline*-4-*carboxylate*.—The foregoing amido-acid (0·5 g.) was heated with refluxing ethanolic hydrogen chloride (100 c.c. of 3%) for 4 hours. The reddish solution was then evaporated, the residue treated with water, and the solid (0·4 g.) collected and washed with alcohol. The product was very sparingly soluble, dissolving only in warm aqueous sodium carbonate and in alcoholic hydrogen chloride. Precipitation from the latter with water gave the *ester* as a white microcrystalline powder, m. p. 258° (decomp.) (Found after drying at 80° in a vacuum: C, 59·4; H, 4·6; N, 10·9. $C_{13}H_{12}O_4N_2$ requires C, 60·0; H, 4·6; N, 10·8%).

2-*Hydroxyquinoline*-3 : 4-*dicarboxylic Acid* (III, R = OH) (cf. Zrike and Lindwall, *loc. cit.*).—The above amido-acid (1 g.) dissolved in the minimum of 40% sulphuric acid (*ca.* 10 c.c.) was cooled to 0° and treated with a concentrated solution of sodium nitrite in water. The yellow solution had turned green at the end point, and on standing and dilution with water a pale yellow solid appeared. This could be crystallised from boiling water giving the quinolinedicarboxylic acid in short colourless needles (0·5 g.), m. p. >325° (Found after drying at 100° in a vacuum: C, 57·1; H, 3·0; N, 6·2. Calc. for $C_{11}H_7O_5N$: C, 56·7; H, 3·0; N, 6·0%).

2-*Hydroxytetrahydroquinoline*-4-*carboxylic Acid*.—The hydroxyquinolinedicarboxylic acid (0·6 g.) was heated on a steam-bath with acetic acid (15 c.c.) and zinc dust (1·5 g.). After 1½ hours the suspension was filtered, and the filtrate diluted with water (10 c.c.) and left overnight. 2-Hydroxytetrahydroquinoline-4-carboxylic acid separated in long colourless needles which after crystallisation from water had m. p. 219°, as recorded by Zrike and Lindwall (*loc. cit.*) (Found: C, 63·4; H, 4·6; N, 7·1. Calc. for $C_{10}H_9O_3N$: C, 62·9; H, 4·7; N, 7·3%).

2 : 4-*Dihydroxy*-1 : 3-*diaza-acridine-5-carboxyl Chloride* (II, R = COCl).—The dried carboxylic acid (1 g.) was heated with thionyl chloride under reflux for 1 hour. Hydrogen chloride was evolved and the mixture became bright yellow. Excess of thionyl chloride was removed under diminished pressure leaving the *acid chloride* as a yellow powder, decomp. 250°. It could not be crystallised, though slightly soluble in boiling dioxan and acetic acid, and it was well washed with ethyl acetate before analysis (Found : Cl, 12·2. $C_{12}H_6O_3N_3Cl$ requires Cl, 12·8%). Reaction with methanol as described in the preparation of the ethyl ester (below) gave the known methyl diaza-acridinecarboxylate (Found : C, 57·2; H, 3·5; N, 14·9. Calc. for $C_{13}H_9O_4N_3$: C, 57·6; H, 3·3; N, 15·5%).

Ethyl 2 : 4-*Dihydroxy*-1 : 3-*diaza-acridine-5-carboxylate* (II, R = CO_2Et).—The acid chloride (1 g.) was heated with ethanol (100 c.c.) under reflux for 2—3 hours. The solution originally yellow was then virtually colourless, and on cooling a pale yellow crystalline solid (0·7 g.) separated. This was insoluble in sodium hydrogen carbonate solution, but dissolved in boiling dioxan, from which the *ethyl* ester separated on adding water as a microcrystalline powder, m. p. >320° (Found : C, 59·2; H, 4·1; N, 14·5. $C_{14}H_{11}O_4N_3$ requires C, 59·0; H, 3·9; N, 14·7%).

2 : 4-*Dihydroxy*-1 : 3-*diaza-acridine-5-carboxyamide* (II, R = $CO{\cdot}NH_2$).—The diaza-acridine acid chloride (4 g.) was added to aqueous ammonia (300—400 c.c., *d* 0·88) which was gently heated under reflux. At first a clear solution was obtained, but within ½ hour solid separated, which was collected after the addition of water. The resulting *amide* (2·5 g.) did not dissolve in aqueous sodium hydrogen carbonate but formed with sodium carbonate a sparingly soluble salt. The amide was precipitated from its solution in warm sodium carbonate by carbon dioxide, and if crystallised from formamide separated in a mass of colourless minute needles, m. p. >310° (Found after drying at 100° in a vacuum : C, 56·3; H, 3·3; N, 21·2. $C_{13}H_8O_3N_4$ requires C, 56·1; H, 3·1; N, 21·8%).

5-*Amino*-2 : 4-*dihydroxy*-1 : 3-*diaza-acridine* (II, R = NH_2).—The suspension of sodium salt obtained on cooling a solution of the diaza-acridine-5-carboxyamide (2·6 g.) in warm 2N-sodium hydroxide (20 c.c., 2 mols.) was treated with sodium hypobromite prepared by dissolving bromine (1·6 g.) in 2N-alkali (20 c.c.). After 3 hours at room temperature the residual solid was collected; it was identified as the amide sodium salt by treating it with mineral acid and recrystallising the product from formamide (Found : C, 56·1; H, 3·3%). Sodium hydroxide (8—10 g.) was added to the dark orange filtrate and the liquid was then gradually heated and maintained at 80° for 1—2 hours. The aminodiaza-acridine (1 g.) was precipitated from the cold solution by neutralisation with acetic acid. Although very sparingly soluble in alcohols, esters, etc., it dissolved freely in warm formamide, but on cooling the solution formed a gel. The product was readily dissolved by hot 2N-hydrochloric acid from which the *hydrochloride* separated in clusters of colourless prisms, m. p. >300° (Found after recrystallising from water and drying in a vacuum at 100° : C, 50·1, 50·3; H, 3·7, 3·4; Cl, 13·2. $C_{11}H_8O_2N_4,HCl$ requires C, 49·9; H, 3·4; Cl, 13·4%).

3 : 3-*Di*-(5-*barbituryl*)-1-*methyloxindole* (I, R = Me).—1-Methylisatin (8·05 g., 1 mol.), prepared by the method of Borsche and Jacobs (*Ber.*, 1914, **47**, 361) and separated from the less soluble isatin by shaking with a small quantity of chloroform, was dissolved in boiling water (30—35 c.c.) with the addition of a little ethanol. Barbituric acid (12·8 g., 2 mol.) was introduced and the mixture heated until a clear solution resulted; concentrated hydrochloric acid (8 c.c.) was then added.

After further heating a solid was precipitated, which was collected and washed with alcohol. To purify the very sparingly soluble *dibarbituryl*-1-*methyloxindole*, it was dissolved in aqueous sodium hydrogen carbonate and precipitated with hydrochloric acid; if acetic acid is used, fairly concentrated solutions give a sodium salt which separates in flat rectangular prisms. 3 : 3-Di-(5-barbituryl)-1-methyloxindole forms colourless rhombohedra, m. p. 250° (decomp.) (Found after drying at 100° in a vacuum : C, 50·9; H, 3·6; N, 17·2. $C_{17}H_{13}O_7N_5$ requires C, 51·1; H, 3·3; N, 17·6%). As with the lower homologue, heating with water effects hydrolysis to the original components.

Methyl 2 : 4-*Diketo*-10-*methyl*-2 : 3 : 4 : 10-*tetrahydro*-1 : 3-*diaza-acridine-5-carboxylate* (VI, R = Me).—Methanolic hydrogen chloride (200 c.c. of 8%) containing the dibarbituryImethyloxindole (8 g.) was refluxed for 5 hours. The cold solution was filtered from a small residue (0·55 g.) and the orange-yellow filtrate evaporated. The remaining solid was washed with sodium hydrogen carbonate solution and dissolved in a large volume of boiling water; the *methyl* ester (VI, R = Me) (2·3 g.) separated on cooling as a mass of brilliant yellow fine prisms, m. p. 280—282° (Found : C, 58·8; H, 4·0; N, 14·4. $C_{14}H_{11}O_4N_3$ requires C, 59·0; H, 3·9; N, 14·7%). The sodium hydrogen carbonate washings contained unchanged dibarbiturylmethyloxindole (3·5 g.). The bright yellow solution of the ester in aqueous sodium hydroxide was only feebly fluorescent, but in acetic acid and alcohol it fluoresced brilliant yellow-green.

2 : 4-*Diketo*-10-*methyl*-2 : 3 : 4 : 10-*tetrahydro*-1 : 3-*diaza-acridine-5-carboxylic Acid* (VI, R = H).—(*a*) The methyl ester (1 g.) was heated under reflux with 2N-sodium hydroxide (15 c.c.) for 20 minutes; the originally orange solution had then become light yellow. On cooling, a sodium salt separated as a thick paste which with careful acidification gave a deep yellow crystalline powder (*ca.* 1 g.). By dissolving in warm sodium hydrogen carbonate solution and precipitating with hydrochloric acid, the very sparingly soluble *methyldiaza-acridine-5-carboxylic acid* was obtained as microscopic yellow short prisms, m. p. >300° (Found : C, 57·7; H, 3·7; N, 15·7. $C_{13}H_9O_4N_3$ requires C, 57·6; H, 3·3; N, 15·5%).

(*b*) When the methyloxindole derivative (I, R = Me) (5 g.) was heated under reflux for 3 hours with concentrated hydrochloric acid (40 c.c.), a trace of *n*-octanol being added to prevent frothing, the 2 : 4-diketo-10-methyl-2 : 3 : 4 : 10-tetrahydro-1 : 3-diaza-acridine-5-carboxylic acid was again formed. It was isolated by evaporating the mineral acid, washing the residue with water, and shaking with warm dilute sodium hydrogen carbonate, the filtered solution (charcoal) depositing the microcrystalline yellow product on acidification (Found : C, 57·4; H, 3·6; N, 15·5%). The acid formed with saturated sodium hydrogen carbonate solution a yellow mass of hair-fine needles, which dissolved in water to form a brilliant blue-green fluorescent solution. The sodium salt obtained with sodium hydroxide does not separate but gives a yellow solution fluorescing green. The fluorescence in acetic acid is green-yellow and in ethanol blue. In sulphuric acid solution the diaza-acridine gives only a pale straw-yellow colour.

Ethyl Benzoylmalonate (cf. Bulow and Hailer, *Ber.*, 1902, **35**, 934).—Powdered sodium (11·5 g., 2 mols.) and ethyl malonate (40 g., 1 mol.) in dry ether (500 c.c.) were heated under reflux to complete the form-

ation of sodium salt. The suspension was shaken while benzoyl chloride (35 g., 1 mol.) was added, and the mixture was then set aside for 24 hours. After addition of water (700 c.c.) and a slight excess of hydrochloric acid, the ether layer was removed, dried, and evaporated. Distillation gave ethyl benzoylmalonate (40 g., 60%), and *ethyl dibenzoylmalonate* (6 g., 6·5%), b. p. 186°/0·03 mm., as a pale yellow opalescent oil (Found: C, 68·3; H, 5·7. $C_{21}H_{20}O_6$ requires C, 68·4; H, 5·4%). The monobenzoyl ester (4 g., 1 mol.) treated with ethylamine (0·68 g., 1 mol.) in dry ether deposited the *ethylamine* derivative (4·6 g., 98%). This dissolved freely in water and alcohol, and crystallised from ethanol–petroleum in long needles, m. p. 92° (Found: C, 62·35; H, 7·4; N, 4·4. $C_{14}H_{16}O_5,C_2H_7N$ requires C, 62·1; H, 7·4; N, 4·5%). Heating to 120° for 30 minutes gave ethyl malonate and *N*-ethylbenzamide.

5-Benzyldialuric Acid.—5-Benzylbarbituric acid (Kast, *Ber.*, 1912, **45**, 3124) (2 g.) and chromic acid (1·4 g.) were heated in refluxing acetic acid (30 c.c.) for 2 hours. Removal of the solvent under reduced pressure left a green friable gum which was dissolved in boiling water (50 c.c.). From the cold solution *5-benzyldialuric acid* (3·6 g., 67%) crystallised in large colourless plates which after crystallisation from water had m. p. 213—215° (slight decomp.) (Found: C, 56·0; H, 4·4; N, 12·1. $C_{11}H_{10}O_4N_2$ requires C, 56·4; H, 4·3; N, 12·0%).

Ethyl 5-Phenyl-2-methylpyrimidine-4-carboxylate (VII).—A solution of sodium (0·25 g., 1 mol.) in alcohol (75 c.c.), acetamidine hydrochloride (1 g., 1 mol.) and ethyl ethoxymethylenebenzoylacetate (Feist, Delf, and Langenkamp, *Ber.*, 1926, **59**, 2958) (2·6 g., 1 mol.) were heated under reflux for 5 hours. The deposit of sodium chloride was removed, the solution evaporated, and the residue distilled, giving *ethyl 5-phenyl-2-methylpyrimidine-4-carboxylate* (1·8 g., 69%) as a colourless oil, b. p. 115°/0·04 mm. (Found: C, 69·7; H, 6·0. $C_{14}H_{14}O_2N_2$ requires C, 69·4; H, 5·8%).

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113. *The Decomposition Reactions of Sodium Aryldiazoates. Part I. Replacement of the Diazo- by the Nitro-group in Alkaline Solution with Sodium Nitrite.*

By HERBERT H. HODGSON and EDWARD R. WARD.

A general reaction is described in which a diazotised amine reacts in alkaline solution with sodium nitrite to give the corresponding nitro-compound, thereby involving replacement of the diazo- by the nitro-group. Examples given are: aniline, *p*-toluidine, *p*-chloroaniline, *o*-nitroaniline, sodium *p*-nitrophenylnitrosoamine, β-naphthylamine, and 4-nitro-1-naphthylamine.

A NUMBER of reactions of aromatic diazo-compounds under aqueous neutral or alkaline conditions have been recently described, and their interpretation based on the occurrence of neutral radicals. The present authors believe, however, that the results can generally be satisfactorily explained on simple polar conceptions. In particular, reference is made to the paper " Some non-ionic Reactions of Diazobenzene Hydroxide " (Waters, *J.*, 1937, 201) in which it was claimed that when an alkaline solution of benzenediazonium sulphate was allowed to decompose slowly a trace of benzene was obtained. This production of benzene was explained as follows: " Hence the intermolecular decomposition of diazobenzenehydroxide possibly does include the hydrogenation of some of the free radicals by other of the aromatic molecules, though as an alternative it may be suggested that free phenyl radicals can abstract hydrogen from water molecules, $Ph^* + H_2O \longrightarrow Ph{:}H + {}^*OH$, a process which is the reverse of the usual breakdown of aqueous solutions of diazonium compounds to give phenols."

If the observation of the trace of benzene were correct, it indicates, on an alternative viewpoint, the presence of a reducing agent at some stage of the complex reaction. Now the only substance of this character appears to be sodium nitrite, which may have been formed by hydrolysis of the sodium phenylnitrosoamine, $C_6H_5{\cdot}\overset{-}{N}(NO)\}\overset{+}{Na}$, present in the alkaline solution, or been present from the start, since no reference is made in the experiment to removal of the slight excess of nitrous acid after diazotisation. The nitrosoamine ion might also have been concerned in the reduction. Further, if benzene had been produced in the manner suggested by the attack of the phenyl radical on water, a much larger amount than a trace might have been anticipated. To ascertain whether sodium nitrite had any effect *per se*, a large amount of it was dissolved in the alkaline diazoate solution, and, after being kept overnight, the mixture was steam distilled, and about 11% of nitrobenzene was obtained. The experiment was then repeated without further addition of sodium nitrite other than the amount required for complete diazotisation, and, after being kept overnight, the mixture was heated for 1 hour on the water-

bath (*vide* Waters, *loc. cit.*) and then (*a*) steam distilled, (*b*) solvent-extracted in a second experiment. In both cases nitrobenzene was formed, and since it gives the same tests as those recorded by Waters for benzene (*loc. cit.*), it was necessary to remove it before testing for benzene (by acid reduction to aniline). Repeated experiments have failed to establish the presence of benzene. Furthermore, experiments in which insufficient nitrous acid was used, thereby entailing the formation of some diazoaminobenzene on making the diazotisation mixture alkaline, failed to give any benzene. In the circumstances we believe that the " benzene " of the Waters experiment was, in fact, nitrobenzene.

Phenol is stated by Waters not to be a major product of the decomposition, but in experiments carried out by Hodgson and Marsden (*J. Soc. Dyers and Col.*, 1945, **61**, 20) on the decomposition of diazotised aniline at the six approximate pH values of 10·5, 8·8, 6·7, 5·3, 5·2 and 4·2, phenol is not only the major product of the decomposition but at the time of formation it has coupled in varying amounts with any unchanged benzenediazohydroxide to give benzeneazo-, -bisazo-, and -trisazo-phenol. These experiments were carried out at pH values lower than that of Waters's experiment (by calculation on the assumption that his aniline sulphate had the formula $C_6H_5{\cdot}NH_2,H_2SO_4$), and therefore were nearer the conditions for obtaining the maximum amount of benzenediazohydroxide.

To ascertain whether the sodium nitrite reaction was a general one, the experiments, with suitable modifications for the amines concerned, were carried out with *p*-toluidine, *p*-chloroaniline, *o*-nitroaniline, β-naphthylamine, and 4-nitro-1-naphthylamine. In each case, nitrocompounds were obtained which indicated replacement of the diazo- by the nitro-group. To avoid auto-coupling in the experiments with β-naphthylamine and 4-nitro-1-naphthylamine, the diazo-solution was dropped gradually into a boiling solution of sodium nitrite containing sodium hydroxide through which a current of steam was passing, whereby the slowly volatile 2-nitro- and 1 : 4-dinitro-naphthalene were removed in sufficient amounts to show that some replacement had occurred.

For the case of *p*-nitroaniline, the sodium salt of *p*-nitrophenylnitrosoamine, $NO_2{\cdot}C_6H_4{\cdot}\overset{\overset{|}{NO}}{N}\}Na$, was isolated and steam distilled with sodium nitrite. At first *p*-dinitrobenzene came over, but after a time the reaction slackened and then ceased altogether; this inhibition was traced to the increased alkalinity of the flask liquor whereby the sodium nitrosoamine had been stabilised, *i.e.*, prevented from hydrolysing according to the scheme :

$$p\text{-}NO_2{-}C_6H_4{-}\overset{\overset{|}{NO}}{N}\}Na + H_2O \rightleftharpoons p\text{-}NO_2{-}C_6H_4{-}N{=}N{-}OH + NaOH$$

$$\Downarrow$$

$$p\text{-}NO_2{-}C_6H_4{-}\overset{\overset{||}{N}}{N}\}OH$$

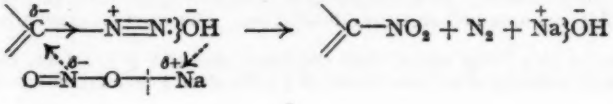
This increased alkalinity is due to the development of sodium hydroxide during the replacement :

$$p\text{-}NO_2{-}C_6H_4{-}N{\equiv}N\}OH + NaNO_2 \longrightarrow p\text{-}NO_2{-}C_6H_4{-}NO_2 + N_2 + NaOH$$

The experiment with diazotised *o*-nitroaniline made slightly alkaline after diazotisation and steam distilled with sodium nitrite, gave a similar cessation of reaction due to the same cause, *viz.*, development of free alkali.

In all the experiments recorded, the respective reduction products, *viz.*, toluene, chlorobenzene, nitrobenzene, naphthalene, and α-nitronaphthalene were never detected despite close search for them, thereby supporting our belief that nitrobenzene and not benzene was the compound obtained in the original experiment by Waters (*loc. cit.*).

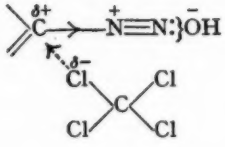
The reaction between sodium nitrite and a diazo-compound in dilute sodium hydroxide solution is thus similar to that of the replacement of a diazo- by a nitro-group in a diazonium cobaltinitrite (Hodgson and Marsden, *J.*, 1944, 22), *viz.*, attack at the significant carbon atom of the diazonium ion by the anionoid O—N=O group :

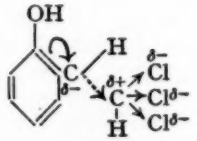


and appears to be a general one. There is no need to keep the alkaline diazo-solution, and steam distillation can be carried out immediately the reactants are mixed.

The work of Bamberger and Storch (*Ber.*, 1893, **26**, 471, 476) on the oxidation of diazo-compounds in alkaline solution includes examples of the formation of nitrobenzene from diazotised aniline which can be ascribed to direct oxidation, since overwhelming amounts of oxidising agents—*e.g.*, for 10 g. of aniline, 71 g. of potassium ferricyanide or *ca.* 100 g. of potassium permanganate—were used and left in contact with the alkaline diazoate for periods of at least 4 days, after which only a trace of nitrobenzene was recorded. This is in striking contrast to the immediate formation of substantial amounts of nitrobenzene and of other nitro-compounds in the present experiments. Any idea of oxidation of the diazo-compounds to nitro-compounds by the sodium nitrite can therefore be eliminated as an alternative mechanism in the experiments now recorded.

The reaction of sodium benzenediazoate with carbon tetrachloride to give chlorobenzene as reported by Hey for Waters's paper (*loc. cit.*, p. 2015) can be simply interpreted in like manner, *viz.*, attack by anionoid chlorine at the carbon atom to which the diazonium group is attached (cf. the converse Reimer–Tiemann reaction, where kationoid carbon attacks the anionoid ortho–para positions in a phenol); there is no need to invoke any free radical hypothesis to explain these various reactions.





(Reimer–Tiemann reaction.)

In the aniline experiment with excess of sodium nitrite, *ca.* 6% of diphenyl was isolated; this would seem to indicate that acceptance of an electron by the diazonium ion was taking place to some extent without resultant combination of the radical so formed with the donor, and that, in the subsequent elimination of nitrogen from the diazo-radical to give the phenyl radical, two of these combine to give diphenyl.

Experimental.

Aniline Decompositions.—(a) *With excess sodium nitrite.* Aniline (0·1 g.-mol.) dissolved in a mixture of sulphuric acid (0·15 g.-mol.; *d* 1·84) and ice-water (200 g.) was diazotised by the gradual addition of sodium nitrite (0·1 g.-mol.) dissolved in the least amount of water until the positive test with starch–potassium iodide paper was obtained. After filtration, the filtrate was made just alkaline to Congo-red by careful addition at 0° of 10% aqueous sodium hydroxide, at which stage sodium nitrite (50 g.) was dissolved in the mixture. Decomposition was rapid even at 0°, and, after keeping overnight, the volatile reaction products were removed by steam distillation. The cooled steam distillate was extracted with ether, and the ether removed from the extract. On subsequent fractionation of the residue, pure nitrobenzene (1·35 g.; *ca.* 11% yield) and diphenyl (0·5 g.; *ca.* 6% yield) were obtained, leaving a small amount which boiled above 260°.

(b) *Without addition of excess sodium nitrite.* A trace of nitrobenzene was obtained both by steam distillation and also by solvent-extraction following the procedure of Waters (*loc. cit.*); it was identified by acid reduction to aniline and subsequent conversion into benzeneazo-β-naphthol. After removal of nitrobenzene as aniline from the solvent extract, no benzene could be detected by nitration or other methods.

Similar Decompositions afforded by other Amines.—(*a*) *p*-Toluidine (3·6 g.) was diazotised as for aniline, with corresponding quantities, and the alkaline solution treated with sodium nitrite (20 g.). Decomposition was rapid even in the cold, and, after 3 hours, the mixture was steam distilled, and a solid (0·4 g.) passed over. This was reduced with tin and hydrochloric acid; most of the solid dissolved, and on steam distillation of the mixture there passed over a small amount of a strong-smelling white solid which was probably *pp'*-ditolyl; on the flask liquor being made alkaline and then steam distilled, *p*-toluidine passed over and was identified by m. p. and conversion into *p*-tolueneazo-β-naphthol. The main product of the reaction was thus *p*-nitrotoluene in *ca.* 9% yield.

(*b*) *p*-Chloroaniline (4·3 g.) in like manner afforded *p*-chloronitrobenzene (0·5 g., *ca.* 9% yield).

(*c*) *o*-Nitroaniline (7 g.), when treated as above, gave an alkaline solution which only decomposed slowly in the cold, and on steam distillation after 1 hour afforded *o*-dinitrobenzene (0·3 g., *ca.* 4% yield). The reaction gradually ceased as the alkalinity developed.

(*d*) *p*-Nitroaniline. Sodium *p*-nitrophenylnitrosoamine (20 g.) was dissolved in water (600 c.c.) and sodium nitrite (20 g.) added; no decomposition occurred in the cold, but pure *p*-dinitrobenzene (1·8 g.; *ca.* 10% yield) was obtained on steam distillation. The reaction gradually ceased as alkalinity developed.

(*e*) β-Naphthylamine (5 g.) was mixed with sulphuric acid (5·8 g.; *d* 1·84) and ice–water (50 g.), and diazotised by rapid addition of sodium nitrite (3 g.) dissolved in the minimum of water; the filtered

solution was then added dropwise to a boiling solution of sodium nitrite (25 g.) in water (100 c.c.) containing 10% aqueous sodium hydroxide (15 c.c.) through which a current of steam was passing. 10% Aqueous sodium hydroxide was added as required to maintain alkalinity. Pure β-nitronaphthalene (0·4 g.; *ca.* 7% yield) passed over, but no naphthalene was present in the distillate.

(*f*) 4-Nitro-1-naphthylamine (5 g.) was treated in similar manner, and afforded sufficient 1 : 4-dinitronaphthalene for its identification.

All the nitro-products referred to were identified by comparison with authentic specimens.

The authors are indebted to the Department of Scientific and Industrial Research for a Senior Research Award to one of them (E. R. W.), and to Imperial Chemical Industries Ltd., Dyestuffs Division, for gifts of chemicals.

TECHNICAL COLLEGE, HUDDERSFIELD. [*Received, May 9th,* 1947.]

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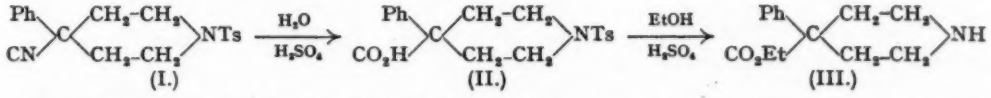
114. *Search for New Analgesics. Part II. Further Homologues of Pethidine and the Pharmacology of these and other Compounds.*

By R. H. THORP and E. WALTON.

This paper describes the preparation of norpethidine by route (I) ⟶ (II) ⟶ (III), and its alkylation to *N*-methyl (pethidine), *N*-ethyl, *N*-*n*-propyl, N-n-iso*propyl*, *N*-*n*-butyl, N-sec.-*butyl*, N-n-*amyl*, N-1-*methylbutyl*, and N-*allyl* derivatives.

The toxic, spasmolytic, and analgesic activity of these compounds and of a number of related lactones and pyrrolidones, described in Part I (*loc. cit.*), is also discussed.

FOLLOWING the discovery of pethidine (Eisleb and Schaumann, *Deut. med. Woch.*, 1939, **65**, 967), the pharmacology, but not the chemistry, of a considerable number of its derivatives, including some *N*-alkyl homologues, has been described by Schaumann (*Arch. exp. Path. Pharm.*, 1940, **196**, 109) and by Eisleb (*Medizin u. Chemie*, 1942, 213). Before these results were fully available in this country, however, we prepared a short series of *N*-alkyl homologues of pethidine, some of which have not apparently been examined by the German workers. A few of these compounds had previously been synthesised by ring closure of ethyl αα′-bis-(β′-bromoethyl)phenylacetate with the appropriate primary amine (Walton and Green, Part I, *J.*, 1945, 315), but in general it was found more convenient to prepare the required homologues by *N*-alkylation of norpethidine (III).



Norpethidine was originally obtained by Eisleb in two ways: (*a*) from 4-cyano-1-benzyl-4-phenylpiperidine by hydrolysis and esterification followed by debenzylation (B.P. 501,135), and (*b*) from 4-cyano-1-*p*-tosyl-4-phenylpiperidine (I) by combined hydrolysis and esterification using sulphuric acid (*Ber.*, 1941, **74**, 1446). The latter process has now been examined in more detail. Treatment of the cyanide (I) with moderately concentrated sulphuric acid failed to remove the tosyl group, but gave 1-p-*tosyl*-4-*phenylpiperidine*-4-*carboxylic acid* (II) in good yield. On the other hand, the tosyl group was readily removed from the acid (II) by alcoholysis yielding norpethidine, which was readily isolated in the form of its carbonate. Preliminary attempts to bring about direct alcoholysis of the cyanide (I) were unsuccessful, owing to its comparative insolubility in alcohol.

Norpethidine was alkylated in the usual manner to give its *N*-methyl, *N*-ethyl, *N*-*n*-propyl, N-iso*propyl*, *N*-*n*-butyl, N-sec.-*butyl*, N-n-*amyl*, N-1′-*methylbutyl*, and N-*allyl* homologues. It was also readily methylated to pethidine by means of formaldehyde and formic acid.

These compounds and many of those described in Part I (*loc. cit.*) have been submitted to a preliminary pharmacological examination particularly with a view to possible analgesic activity.

Toxicity determinations were made by intravenous injection in mice, using 25 mice for each experiment. The values given in the Table are an assessment of the LD. 50 made from the observed percentage mortalities resulting from doses close in value to the figure stated.

Analgesic activity was estimated by the method described by one of us (R. H. T.) (*Brit. J. Pharmacol.*, 1946, **1**, 113), in which the pain threshold of rats to radiant heat is determined. Tests were carried out on groups of 9 rats, each compound being used three or four times at different dose levels. The pain threshold values were determined ½, 1, 2, and 3 hours after injection in order to get an index at the duration of action, and the maximum increase in pain

threshold has been used in the comparisons. Pethidine and morphine were used as standards of comparison in all the experiments, and the results given in the second column of the Table represent relative analgesic activities (taking morphine as unity) derived from the doses causing approximately a 50% increase in the pain threshold.

The compounds were tested for spasmolytic activity using an isolated preparation of the rabbit small intestine and inducing spasm with carbaminoylcholine and barium chloride. Certain of these substances were also tested on œstrogenic uterine segments from immature female rabbits, caused to contract with adrenaline. The results of these spasmolytic tests are also given in the Table, each figure being the average of six to ten tests upon different muscle segments.

Compound (as hydrochloride).	Toxicity I.V. mice, mg./kg.	Analgesic activity (morphine = 1).	Spasmolytic activity (dilution × 1000). Rabbit ileum. Carbaminoyl-choline.	Rabbit ileum. Barium chloride.	Œstrogenic uterus adrenaline.
Pethidine [1,2]	60	0·1—0·13	500	500	200
4-Phenyl-1-methylpiperidine-4-carboxyamide [2,3]	—	nil	50	10	—
Norpethidine [1,2]	65	0·05	150	—	—
N-Ethylnorpethidine [3]	—	0·05	200	—	—
N-*n*-Propylnorpethidine [3]	40	0·15—0·2	200	—	—
N-*iso*Propylnorpethidine	50	0·05	500	—	—
N-*n*-Butylnorpethidine [3]	25	0·15	150	—	—
N-*sec*.-Butylnorpethidine	30	0·12	100	—	—
N-*n*-Amylnorpethidine	12	0·15	—	—	—
N-1′-Methylbutylnorpethidine	—	0·05	—	—	—
N-Allylnorpethidine	50	0·08	150	—	—
N-Benzylnorpethidine [1,3]	17	0·05	50	—	—
α-Phenyl-α-(β′-aminoethyl)butyrolactone [3]	20	Nil	10	10	Nil
α-Phenyl-α-(β′-methylaminoethyl)-butyrolactone [3]	120	Nil	5	10	10
α-Phenyl-α-(β′-ethylaminoethyl)-butyrolactone [3]	10	Nil	10	10	10
α-Phenyl-α-(β′-diethylaminoethyl)-butyrolactone [3]	—	Nil	—	—	—
α-Phenyl-α-(β′-*n*-propylaminoethyl)-butyrolactone [3]	90	Nil	20	10	10
α-Phenyl-α-(β′-piperidinoethyl)butyrolactone [3]	40	Nil	5,000	2,000	10
α-Phenyl-α-(β′-benzylmethylaminoethyl)butyrolactone [3]	—	Nil	—	—	—
3-Phenyl-3-(β-aminoethyl)-2-pyrrolidone [3]	—	Nil	8	Enhanced contraction	10
3-Phenyl-3-(β-methylaminoethyl)-2-pyrrolidone [3]	20	Nil	10	Enhanced contraction	10
Trasentin	—	—	10,000	2,000	200
Atropine	—	—	100,000	20,000	—

[1] Eisleb, *Ber.*, 1941, **74**, 1446. [2] B.P. 501,135. [3] Part I, *loc. cit.*

It will be seen from the Table that the toxicity of the alkyl homologues of pethidine increases with the length of the alkyl chain and that analgesic activity increases slightly up to the *n*-propyl compound, which is definitely rather more active than pethidine. The butyrolactone compounds show no analgesic action and, with the exception of the piperidine compound, α-phenyl-α-(β′-piperidinoethyl)butyrolactone hydrochloride, are only poorly spasmolytic. The two pyrrolidones are not analgesic and have no very appreciable spasmolytic action.

It can be concluded that lactones and pyrrolidones of these types are unlikely to prove to be substances of therapeutic value and that the *N*-alkyl homologues of pethidine, although some show slightly greater activity as analgesics, are not sufficiently different from, or more potent than, pethidine to prove of greater value.

Experimental.

1-p-*Tosyl*-4-*phenylpiperidine*-4-*carboxylic Acid* (II).—4-Cyano-1-*p*-tosyl-4-phenylpiperidine (Eisleb, *Ber.*, 1941, **74**, 1446) (50 g.), concentrated sulphuric acid (30 ml.), and water (15 ml.) were heated under reflux until the cyanide had dissolved. The solution was then treated with water (20 ml.) and dilution continued at a rate such as to maintain a clear solution. (Total addition of water, about 200 ml.; total

time of reflux, 3 hours.) On cooling, 1-p-*tosyl*-4-*phenylpiperidine*-4-*carboxylic acid* (52 g., 98%) separated. It crystallised from water in rectangular plates, m. p. 228—231° (Found: N, 3·9; S, 8·6. $C_{19}H_{21}O_4NS$ requires N, 3·9; S, 8·9%).

Ethyl 4-*Phenylpiperidine*-4-*carboxylate* (*Norpethidine*) (III).—The acid (II) (10 g.), ethyl alcohol (30 ml.), and sulphuric acid (6 ml.) were refluxed for 3 hours. The solution was poured into water (100 ml.), made strongly alkaline, and extracted with ether. The ethereal solution, on treatment with carbon dioxide, gave *norpethidine carbonate* as a voluminous white solid, which tended to decompose on attempted crystallisation from water, alcohol, and other solvents (Found: C, 68·0; H, 7·6; N, 5·7. $C_{14}H_{19}O_2N,\frac{1}{2}H_2CO_3$ requires C, 65·9; H, 7·6; N, 5·3%). Norpethidine hydrochloride, from the carbonate, crystallised from alcohol–ether in hexagonal tablets, m. p. 134—135° (Found: N, 5·6; Cl, 12·8. Calc. for $C_{14}H_{19}O_2N,HCl$: N, 5·2; Cl, 13·2%).

Ethyl 4-*Phenyl*-1-*methylpiperidine*-4-*carboxylate* (*Pethidine*).—(*a*) Norpethidine carbonate (7 g.), 40% aqueous sodium hydroxide (4·5 ml.), and sufficient alcohol to produce a homogeneous solution were treated slowly with methyl iodide (4·3 g.) with shaking, the mixture being subsequently refluxed for 10 minutes. The alcohol was removed, the residue made strongly alkaline, and the ethereal extract treated with hydrochloric acid. By recrystallisation from alcohol–ether the aqueous residue gave pethidine hydrochloride (2·5 g.), m. p. 185°, identical with a genuine specimen.

(*b*) Norpethidine carbonate (5 g.), 36% formaldehyde solution (4·3 ml.), and 98% formic acid (1·7 g.) were warmed at 100° for ½ hour. The mixture was extracted with ether and the ethereal extract treated with carbon dioxide to remove any norpethidine as carbonate. Evaporation of the filtrate and treatment with hydrochloric acid in the usual way gave pethidine hydrochloride in good yield (3·5 g.).

Ethyl 4-*Phenyl*-1-*ethylpiperidine*-4-*carboxylate*.—Norpethidine (7 g.), 40% sodium hydroxide solution (6 ml.), and sufficient alcohol to give a homogeneous solution were treated with ethyl sulphate and the product worked up in the manner described above for pethidine (*a*). The resulting hydrochloride (3·1 g.), m. p. 196°, was identical with a specimen prepared from ethyl αα-bis-(β′-bromoethyl)phenylacetate (Part I, 1945, 317).

Ethyl 4-phenyl-1-*n*-propylpiperidine-4-carboxylate was prepared from norpethidine carbonate (5 g.), 40% sodium hydroxide solution (3·75 ml.), *n*-propyl iodide (3·65 g.), and a little alcohol by refluxing for ½ hour. The hydrochloride, m. p. 196° from alcohol–ether, was identical with an authentic specimen (Part I, *loc. cit.*).

Ethyl 4-*phenyl*-1-iso*propylpiperidine*-4-*carboxylate*. This was prepared in the same way. The crude alkylation product (base) in ether was treated with carbon dioxide to remove unchanged norpethidine as carbonate. The filtrate gave a good yield of the *hydrochloride*, which crystallised from alcohol–ether in leaflets, m. p. 165—166° (Found: C, 64·9; H, 8·2; N, 4·8; Cl, 11·3. $C_{17}H_{25}O_2N,HCl$ requires C, 65·5; H, 8·3; N, 4·5; Cl, 11·4%). Ethyl 4-phenyl-1-*n*-butylpiperidine-4-carboxylate, prepared in the same way, gave a hydrochloride, m. p. 181—183° (cf. Part I, *loc. cit.*).

Ethyl 4-*phenyl*-1-sec.-*butylpiperidine*-4-*carboxylate*. This was made by heating norpethidine carbonate (1 g.), 33% sodium hydroxide solution (1 ml.), and *sec.*-butyl iodide (1·6 g.) in a sealed tube for 1 hour at 100°. No norpethidine was recovered as carbonate. The *hydrochloride* crystallised from alcohol–ether in plates, (0·3 g.), m. p. 179—180° (depression with the *N*-butyl derivative) (Found: C 66·6; H, 8·8; N, 4·8; Cl, 10·9. $C_{18}H_{27}O_2N,HCl$ requires C, 66·4; H, 8·3; N, 4·3; Cl, 10·9%).

Ethyl 4-*phenyl*-1-n-*amylpiperidine*-4-*carboxylate*. This was made by refluxing norpethidine carbonate (1 g.), 33% sodium hydroxide solution (1 ml.), *n*-amyl iodide (1·7 g.), and a little *n*-amyl alcohol for 1 hour. No norpethidine was recovered. The *hydrochloride* separated from alcohol–ether in hexagonal plates (0·8 g.), m. p. 178—179° (Found: C, 67·0; H, 8·9; Cl, 10·6. $C_{19}H_{29}O_2N,HCl$ requires C, 67·2; H, 8·5; Cl, 10·5%).

Ethyl 4-*phenyl*-1-(1′-*methylbutyl*)*piperidine*-4-*carboxylate*. This was made by alkylating norpethidine carbonate with 2-bromopentane in a sealed tube at 100°. Its *hydrochloride* crystallised from alcohol–ether in rectangular prisms, m. p. 175—176° (depression with the *n*-amyl derivative) (Found: N, 4·4; Cl, 10·6. $C_{19}H_{29}O_2N,HCl$ requires N, 4·1; Cl, 10·5%).

Ethyl 4-*phenyl*-1-*allylpiperidine*-4-*carboxylate*. This was made by refluxing norpethidine carbonate (3 g.), 33% sodium hydroxide solution (2·25 ml.), allyl bromide (3 g.), and a little alcohol, for 10 minutes. The *hydrochloride* (0·8 g.) formed plates, m. p. 162—163°, from alcohol–ether (Found: C, 66·0; H, 7·8; N, 4·6; Cl, 11·5. $C_{17}H_{23}O_2N,HCl$ requires C, 65·9; H, 7·8; N, 4·5; Cl, 11·5%).

Thanks are due to Mr. A. Bennett for micro-analyses and to Mr. E. C. Durling for help with the experimental work.

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WELLCOME CHEMICAL WORKS, DARTFORD, KENT. [*Received, May 13th,* 1947.]

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115. *Contributions to the Chemistry of Synthetic Antimalarials. Part VI. Some Derivatives of* 1 : 3 : 5-*Triazine.*

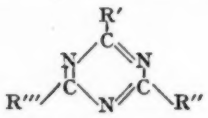
By W. W. CUTHBERTSON and J. S. MOFFATT.

A number of basically substituted 1 : 3 : 5-triazines have been prepared. They exhibit no trypanocidal activity and little or no antimalarial activity.

As part of a programme for the examination of simple heterocyclic nuclei for chemotherapeutic activity several derivatives of 1 : 3 : 5-triazine have been prepared. The 1 : 3 : 5-triazine

nucleus has been the subject of several investigations in the realm of potential therapeutic agents; thus Jensch (U.S.P. 2,092,552) claimed that cyanuric quinoline derivatives were effective in diseases due to bacteria and protozoa. Friedheim (*J. Amer. Chem. Soc.*, 1944, **66**, 1775; U.S.P. 2,295,574) and Controulis *et al.* (*ibid.*, p. 1771) describe some arsenic substituted anilino-triazines, of which 4 : 6-diamino-2-(4′-arsenoanilino)-1 : 3 : 5-triazine has found application in African sleeping sickness (*Schweiz. Med. Woch.*, 1941, **5**, 116); while Controulis (*J. Amer. Chem. Soc.*, 1945, **67**, 1946) states that alkoxy-triazines possess the power to alleviate histamine shock in guinea pigs. While the work now reported was in progress Mosher and Whitmore (*J. Amer. Chem. Soc.*, 1945, **67**, 662) described the synthesis of a number of aminoalkylamino-1 : 3 : 5-triazines most of which contained the γ-piperidinopropylamino-grouping; no biological data, however, were quoted. A number of triazines similar to those now described have since been prepared by Curd, Landquist, and Rose (*J.*, 1947, 154), but none of these exhibited any anti-malarial activity. Some similarly constituted pyrimidines have been described by Curd and Rose (*J.*, 1946, 343); a number of these possess antimalarial activity.

In the present paper three types of triazine compound are described: (*a*) 6-methoxy-8-quinolylamino-, (*b*) δ-diethylamino-α-methylbutylamino-, and (*c*) *p*-chloroanilino-derivatives, the remaining positions in the triazine nucleus being substituted with other groups such as amino-, diethylamino-, *iso*propylamino-, and methoxy- (see Table).



Type.	R′.	R″.	R‴.	Type.	R′.	R″.	R‴.
I	A	NEt_2	Cl	III	C	$NHPr^{\beta}$	Cl
	A	NEt_2	NH_2		C	,,	NH_2
	A	NH_2	NH_2		C	,,	OMe
					C	,,	H
II	B	NH_2	Cl				
	B	NH_2	OMe				

(A = 6-methoxy-8-quinolylamino-; B = δ-diethylamino-α-methylbutylamino-; C = *p*-chloro-anilino-).

Most of the triazines were synthesised from cyanuric chloride in which all three chlorine atoms are reactive and capable of replacement either singly or completely, according to conditions. In general, the first chlorine atom is replaced at 0°, the second at room temperature, and the third at 120—140°. For example, reaction at 25° of 2 : 4-dichloro-6-*p*-chloroanilino-1 : 3 : 5-triazine with 2 mols. of *iso*propylamine in chloroform gave 2-chloro-6-*p*-chloroanilino-4-*iso*propylamino-1 : 3 : 5-triazine. It was difficult to stop at the introduction of one methoxyl group when two or more chlorine atoms were present, owing to the ready reaction of these with alcohol alone. An attempted preparation of 2 : 4-dichloro-6-methoxy-1 : 3 : 5-triazine by reaction of cyanuric chloride at room temperature with one mol. of sodium methoxide in methyl alcohol gave 2 : 4 : 6-trimethoxy-1 : 3 : 5-triazine. On carrying out the reaction at 0° some monomethoxy-product was indeed isolated in one experiment, but the product generally appeared to be a mixture of all three substituted compounds.

Substances of type I gave crystalline salts whereas those of type II failed to do so. Indeed, the free base itself of the compound (R′ = B, R″ = NH_2, R‴ = Cl) could not be obtained in a pure state. On attempted distillation very little material distilled, and the remainder on cooling set to a hard glass which may be a condensation product of two or more molecules formed by elimination of hydrogen chloride.

In the case of substances of type III, an unsuccessful attempt was made to prepare 6-p-*chloroanilino*-4-iso*propylamino*-1 : 3 : 5-*triazine* by selective dechlorination in the hetero-ring of the 2-chloro-derivative. Use of sodium in liquid ammonia (U.S.P. 2,385,761; (*Chem. Abs.*, 1946, **40**, 613)) led to complete dechlorination and the production of 6-*anilino*-4-iso*propylamino*-1 : 3 : 5-*triazine*. Palladium–strontium carbonate and hydrazine (*J.*, 1935, 1283) had a similar effect, while the use of zinc and glacial acetic acid yielded only unchanged starting material. The structure of the completely dechlorinated product was proved by an alternative synthesis from cyanuric chloride by successive treatment with aniline and *iso*propylamine followed by dechlorination in the 6-position.

The substance was eventually obtained by condensation of N^1-*p*-chlorophenyl-N^5-*iso*propyldiguanide with ethyl formate (cf. Rackmann, *Annalen*, 1910, **376**, 170; Wagner, *J. Org.*

Chem., 1940, **5**, 133). Dechlorination yielded the previously obtained 6-anilino-4-*iso*propylamino-1 : 3 : 5-triazine. The above diguanide, which itself possesses a high antimalarial activity, was prepared by the method of Curd and Rose (*J.*, 1946, 729).

Salts of type III were readily hydrolysed and remained in solution only in presence of an excess of acid, although in one case (R′ = *p*-chloroanilino-, R″ = *iso*propylamino-, R‴ = NH_2) a pure *hydrobromide* was isolated. Treatment of 2-p-*chloroanilino*-4-iso*propylamino*-6-*methoxy*-1 : 3 : 5-*triazine* with hydrobromic acid led to demethylation and formation of the corresponding *triazone*, identified by analysis and reconversion into the 6-chloro-compound with phosphoryl chloride.

The substances were tested for therapeutic activity against *Trypanosoma equiperdum* in mice and *Plasmodium gallinaceum* in chicks; no activity was observed, except in the compound (R′ = *p*-chloroanilino-, R″ = *iso*propylamino-, R‴ = H) which had possibly a slight activity against *Plasmodium gallinaceum*.

Experimental.

Cyanuric chloride, m. p. 147°, was prepared by the method of Diels (*Ber.*, 1899, **32**, 691).

2 : 4-*Dichloro*-6-(6′-*methoxy*-8′-*quinolylamino*)-1 : 3 : 5-*triazine* (I).—8-Amino-6-methoxyquinoline (37·7 g.) in chloroform (100 c.c.) was added dropwise to a stirred solution of cyanuric chloride (20 g.) in chloroform (200 c.c.) at 0°. 8-Amino-6-methoxyquinoline hydrochloride separated as an orange powder together with the product. After removal of chloroform by distillation, the residue was extracted several times with boiling benzene. The combined extracts, on cooling, gave fine yellow needles of the *compound* (18·8 g.), m. p. 237° (Found : Cl, 21·7. $C_{13}H_9ON_5Cl_2$ requires Cl, 22·0%).

2-*Chloro*-6-(6′-*methoxy*-8′-*quinolylamino*)-4-*diethylamino*-1 : 3 : 5-*triazine* (II).—Diethylamine (5·6 g.) in chloroform (20 c.c.) was added dropwise to (I) (12·3 g.) in chloroform (50 c.c.) at room temperature. The chloroform solution was extracted with water, and evaporation of the dried solution gave the *compound* (11·5 g.) which crystallised from benzene in colourless prisms, m. p. 170° (Found : N, 23·5; Cl, 9·8. $C_{17}H_{19}ON_6Cl$ requires N, 23·4; Cl, 9·9%). The *hydrochloride* had m. p. 278° (decomp.) (Found : N, 19·25; OMe, 7·2. $C_{17}H_{19}ON_6Cl,HCl,2H_2O$ requires N, 19·4; OMe, 7·2%).

2-*Amino*-6-(6′-*methoxy*-8′-*quinolylamino*)-4-*diethylamino*-1 : 3 : 5-*triazine*.—The above chloro-compound (2·75 g.) was heated with saturated alcoholic ammonia (25 c.c.) in a sealed tube at 140° for 8 hours; the *product* formed yellow needles from alcohol, m. p, 191° (Found : N, 28·9. $C_{17}H_{21}ON_7$ requires N, 28·9%). The *hydrochloride* had m. p. 216° (decomp.) (Found : N, 21·8. $C_{17}H_{21}ON_7,2HCl,2H_2O$ requires N, 21·9%).

2 : 4-*Diamino*-6-(6′-*methoxy*-8′-*quinolylamino*)-1 : 3 : 5-*triazine*.—A mixture of (I) (1 g.) and saturated alcoholic ammonia (10 c.c.) was heated at 130° for 8 hours. The free base separated on cooling; it was insoluble in organic solvents, and was purified as the *hydrochloride*, m. p. 280° (decomp.) (Found : N, 25·0; Cl, 17·5; OMe, 7·6. $C_{13}H_{13}ON_7,2HCl,2H_2O$ requires N, 24·9; Cl, 18·1; OMe, 7·9%).

Attempted Preparation of 2 : 4-*Dichloro*-6-*methoxy*-1 : 3 : 5-*triazine*.—Treatment of cyanuric chloride (1 g.) in dry methanol (10 c.c.) with sodium (0·125 g.) in methanol (10 c.c.) at 0°, followed by distillation of the methanol under reduced pressure at 25°, and recrystallisation of the residue from ethyl acetate, gave a product, m. p. 130° which was obviously the trimethoxy-derivative (Found : OMe, 53·0. Calc. for $C_6H_9O_3N_3$: OMe, 54·3%); literature m. p. 134°.

2 : 4-*Dichloro*-6-*amino*-1 : 3 : 5-*triazine* (III) (Diels, *loc. cit.*).—Cyanuric chloride (5 g.) in dry ether (100 c.c.) was treated at 0° with dry ammonia. Recrystallisation of the product from ether, then benzene, gave colourless needles (3 g.), m. p. 237°.

2-*Chloro*-6-*amino*-4-*methoxy*-1 : 3 : 5-*triazine* (IV).—Sodium methoxide solution (0·42 g. of sodium in 42 c.c. of methanol) at room temperature was added gradually to (III) (3 g.). The product separated as a white mass, which was collected and washed with water to remove sodium chloride. Recrystallisation from ethyl acetate gave colourless plates (1·8 g.), m. p. > 300° (Found : N, 34·9; Cl, 21·8; OMe, 19·35. $C_4H_5ON_4Cl$ requires N, 34·9; Cl, 22·1; OMe, 19·3%).

6-*Amino*-2-(δ-*diethylamino*-α-*methylbutylamino*)-4-*methoxy*-1 : 3 : 5-*triazine*.—A mixture of (IV) (2·9 g.) and δ-diethylamino-α-methylbutylamine (17·4 g.) was heated in a sealed tube at 120° for 4 hours. Excess of diamine was removed by distillation; the viscous brown residue, b. p. 210°/0·1 mm. (3·9 g.), failed to crystallise. Decomposition of the pure *dipicrate*, m. p. 190° (Found : C, 41·0; H, 4·8; N, 22·7. $C_{13}H_{26}ON_6,2C_6H_3O_7N_3$ requires C, 40·5; H, 4·3; N, 22·7%), gave the pure *base* as a pale yellow syrup, b. p. 195—200°/0·03 mm. (Found : N, 29·8. $C_{13}H_{24}ON_6$ requires N, 29·7%).

2-*Chloro*-6-*amino*-4-(δ-*diethylamino*-α-*methylbutylamino*)-1 : 3 : 5-*triazine*.—A solution of (III) (5 g.) in chloroform (50 c.c.) was treated gradually with δ-diethylamino-α-methylbutylamine (9·6 g.) in chloroform (25 c.c.) at room temperature. The solution was extracted with water to remove diamine hydrochloride, and evaporation of the dried solution gave a viscous brown syrup. Only a small amount distilled at 250°/0·3 mm., and the remainder solidified to a hard glass. The latter may be a condensation product of two molecules formed by elimination of hydrogen chloride. The distillate was impure (Found : N, 30·8. $C_{12}H_{22}N_6Cl$ requires N, 29·3%) and failed to give a crystalline picrate, styphnate, or picrolonate.

2 : 4-*Dichloro*-6-p-*chloroanilino*-1 : 3 : 5-*triazine*.—*p*-Chloroaniline (6·9 g.) in chloroform (50 c.c.) was added dropwise to a stirred solution of cyanuric chloride (5 g.) in chloroform (100 c.c.) at 0°. The precipitated *p*-chloroaniline hydrochloride was removed by filtration and washed with chloroform, and the filtrates were extracted with water. Evaporation of the dried solution gave the crude product (7 g.) which crystallised from benzene in colourless microcrystals, (4·2 g.), m. p. 188° (Found : N, 20·3. Calc. for $C_9H_5N_4Cl_3$: N, 20·3%).

2-*Chloro*-6-p-*chloroanilino*-4-iso*propylamino*-1 : 3 : 5-*triazine*.—*iso*Propylamine (3·5 c.c.) in chloroform (25 c.c.) was added gradually to a solution of the above dichloro-compound (5·56 g.) in chloroform (50 c.c.)

at room temperature. The product formed colourless microcrystals (4·6 g.) from benzene, m. p. 172° (Found: N, 23·6. Calc. for $C_{12}H_{13}N_5Cl_2$: N, 23·5%).

2-*Amino*-6-p-*chloroanilino*-4-iso*propylamino*-1 : 3 : 5-*triazine*.—The above chloro-compound (5 g.) was heated with saturated alcoholic ammonia (75 c.c.) at 140° for 8 hours. Evaporation of the alcohol and extraction with chloroform gave a colourless syrup (5·1 g.) which crystallised on trituration with acetone. The *compound* formed colourless microcrystals (3·16 g.) from ethyl acetate, m. p. 166° (Found: N, 29·9; Cl, 12·6. $C_{12}H_{15}N_6Cl$ requires N, 30·2; Cl, 12·7%). The *hemistyphnate* had m. p. 239° (Found: N, 26·1. $2C_{12}H_{15}N_6Cl,C_6H_3O_8N_3$ requires N, 26·2%), and the *hydrobromide*, m. p. 223° (Found: N, 22·5. $C_{12}H_{15}N_6Cl,HBr,H_2O$ requires N, 22·2%). The hydrochloride has been described by Curd, Landquist, and Rose (*loc. cit.*).

6-p-*Chloroanilino*-4-iso*propylamino*-2-*methoxy*-1 : 3 : 5-*triazine*.—2-Chloro-6-*p*-chloroanilino-4-*iso*propylamino-1 : 3 : 5-triazine (2·98 g.) was refluxed with sodium methoxide solution (0·25 g. of sodium in 50 c.c. of methanol) for 4 hours. Evaporation of the alcohol gave a syrup (2·9 g.), b. p. 205°/0·03 mm., which crystallised on trituration with ether. The *compound* crystallised from ether–light petroleum (b. p. 40—60°) in fine needles (1·5 g.), m. p. 137° (Found: N, 23·6; Cl, 12·2. $C_{13}H_{16}ON_5Cl$ requires N, 23·8; Cl, 12·1%). An attempt to prepare the hydrobromide gave material, m. p. 337° (Found: N, 21·55; OMe, 0·85%), which was probably the hydrobromide of 6-*p*-chloroanilino-4-*iso*propylamino-2-triazone. Addition of ammonia to an alcoholic solution of this gave the free *base*, which formed an amorphous white powder from aqueous pyridine, m. p. 365° (Found: N, 24·95. $C_{13}H_{14}ON_5Cl$ requires N, 25·0%). The triazone (1·1 g.) was refluxed for 4 hours with phosphoryl chloride (10 c.c.), and the mixture was poured into ice–water and neutralised with ammonia. Recrystallisation from benzene gave 2-chloro-6-*p*-chloroanilino-4-*iso*propylamino-1 : 3 : 5-triazine, m. p. and mixed m. p. with authentic sample, 170°.

Attempted Preparation of 6-p-*Chloroanilino*-4-iso*propylamino*-1 : 3 : 5-*triazine*.—Sodium (0·4 g.) was added during 1 hour to 2-chloro-6-*p*-chloroanilino-4-*iso*propylamino-1 : 3 : 5-triazine (2·07 g.) in liquid ammonia (40 c.c.). Ammonium chloride (1 g.) was then added, and the ammonia allowed to evaporate. The residue was extracted with hot benzene which, on cooling, deposited crystals (0·77 g.), m. p. 197—198°. Recrystallisation from the same solvent gave 6-*anilino*-4-iso*propylamino*-1 : 3 : 5-*triazine* (Found: C, 62·7; H, 6·6; N, 30·4; Cl, 0·00. $C_{12}H_{15}N_5$ requires C, 62·8; H, 6·5; N, 30·5%). An attempted reduction by zinc and glacial acetic acid in alcohol was carried out as follows. The chloro-compound (2·6 g.), alcohol (75 c.c.), glacial acetic acid (12·5 c.c.), and zinc powder (7·5 g.) were stirred mechanically at room temperature for 8 hours. After standing overnight, a further quantity of acetic acid (10 c.c.) was added and stirring continued for 8 hours. Excess of zinc was removed by filtration, and the filtrate was poured into water and extracted with chloroform. Evaporation of the dried extract gave a crude product (2·3 g.) which, after recrystallisation from benzene, was shown by mixed m. p. to be identical with the starting material.

Reduction by Hydrazine and Palladium–Strontium Carbonate in Alcohol.—A solution of 2-chloro-6-*p*-chloroanilino-4-*iso*propylamino-1 : 3 : 5-triazine (1·72 g.) in alcohol (100 c.c.) was boiled for 30 minutes with alcoholic potassium hydroxide (100 c.c.; 10%), palladised strontium carbonate (10 g.; 2%), and hydrazine hydrate (4 c.c.; 50%). Evaporation of alcohol from the filtered solution, and extraction of the residue with benzene, gave 6-anilino-4-*iso*propylamino-1 : 3 : 5-triazine (0·7 g.), m. p. 199°.

2 : 4-*Dichloro*-6-*anilino*-1 : 3 : 5-*triazine* (Fierz-David and Matter, *J. Soc. Dyers Col.*, 1937, **53**, 424).—This was prepared from aniline (3·1 g.) in chloroform (15 c.c.) and cyanuric chloride (3·15 g.) in chloroform (40 c.c.). It formed colourless needles (2·78 g.) from benzene–light petroleum (b. p. 60—80°), m. p. 136—137° (Found: N, 23·2; Cl, 29·2. Calc. for $C_9H_6N_4Cl_2$: N, 23·2; Cl, 29·4%).

2-*Chloro*-6-*anilino*-4-iso*propylamino*-1 : 3 : 5-*triazine*.—The above dichloro-compound (2 g.) in chloroform (20 c.c.) was treated gradually with *iso*propylamine (1·4 c.c.) in chloroform (10 c.c.). The *product* (1·35 g.) separated in colourless microcrystals from benzene–light petroleum (b. p. 60—80°), m. p. 127—128° (Found: N, 26·3; Cl, 13·25. $C_{12}H_{14}N_5Cl$ requires N, 26·6; Cl, 13·5%).

Dechlorination by hydrazine and palladised strontium carbonate gave 6-anilino-4-*iso*propylamino-1 : 3 : 5-triazine, m. p. 199°, identical with the product obtained previously.

6-p-*Chloroanilino*-4-iso*propylamino*-1 : 3 : 5-*triazine*.—N^1-*p*-Chlorophenyl-N^5-*iso*propyldiguanide (3·2 g.), methyl alcohol (20 c.c.), and ethyl formate (10 c.c.) were heated under reflux for 1 hour. The *product* separated from the mixture and formed colourless microcrystals from methyl alcohol, m. p. 228° (Found: N, 26·6; Cl, 13·75. $C_{12}H_{14}N_5Cl$ requires N, 26·6; Cl, 13·5%). Dechlorination by hydrazine and palladised strontium carbonate furnished 6-anilino-4-*iso*propylamino-1 : 3 : 5-triazine, m. p. 199°.

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116. *Chemistry of the* Coprosma *Genus. Part I. The Colouring Matters from* Coprosma Australis.

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Three colouring matters from the bark of *Coprosma australis* have been identified with the anthraquinone derivatives morindin, morindone, and rubiadin-1 methyl ether, the total yield of the three constituents reaching 17% of the dry weight. The same constituents have been identified in the root bark.

THE genus *Coprosma* with 90 species, one of the largest genera of the *Rubiaceæ* well known for their tinctorial properties, has a predominantly temperate distribution and is developed to its greatest extent in New Zealand where there exist 41 endemic species. The inner bark of numerous species has been used extensively by the Maoris for colouring flax fibre [Te Rangihiroa (Sir Peter Buck), " On the Maori Art of Weaving Cloaks, Capes and Kilts ", Dominion Museum Bulletin (New Zealand), 1911, No. 3]. During the Great War of 1914—1918 when khaki dyes were scarce, Aston (*New Zealand J. Sci. Tech.*, 1918, **1**, 3, 264, 346; *New Zealand J. Agric.*, 1917, **15**, 55, 117; 1918, **16**, 358; 1919, **17**, 136; 1923, **26**, 78) investigated numerous species and found that many had mordant dye properties. He also drew attention to the wide individuality shown by the cortical tissue and the colour produced by the action of dilute sodium hydroxide solution. The dyeing properties of this genus have also been elaborated by Hutchinson (" Plant Dyeing ", Telegraph Print, Napier, New Zealand, 1943) for the home dyer.

C. australis (syn., *C. grandifolia*) is a large shrub 8—15 feet high occurring abundantly from sea level to 2,000 feet throughout the North Island and the Marlborough and Nelson Provinces of the South Island of New Zealand. The bark is coloured orange on the inner surface, and is quite thick and readily stripped from the trunk. The sap from the inner bark has been used by the early Maoris as a cure for scabies (" hakihaki ") (Goldie, *Trans. Roy. Soc. New Zealand*, 1904, **37**, 1) but Skey (*ibid.*, 1869, **2**, 152) could not detect the presence of alkaloids. Aston, however (*New Zealand J. Agric.*, 1017, **15**, 117; 1918, **16**, 358; *New Zealand J. Sci. Tech.*, 1918, **1**, 3), isolated two coloured crystalline compounds *A* and *B* from the stem bark of this species in 0·068% yield. Compound *A* melted at 270—272° and sublimed in iridescent brick-red needles at *ca.* 200° with a violet vapour, while compound *B* melted at 285—286° and sublimed above 200° in canary-yellow crystals. The colour reactions were typical of anthraquinone derivatives but the compounds were not analysed or identified.

In a later investigation on the same plant, Denz (Jacob Joseph Scholarship Thesis, Victoria University College, New Zealand, 1933) separated three compounds, *A*, $C_{14}H_8O_3$, m. p. 302°, which he considered to be β-hydroxyanthraquinone since on fusion with potassium hydroxide it allegedly yielded alizarin, *B*, orange-yellow needles, m. p. 230°, and *C*, for which no details were given.

With the kind permission of Mr. B. C. Aston we are continuing work in this field. The material for this investigation was collected from Kauri Gully, near Auckland. By exhaustive extraction of the air-dried bark with alcohol or acetone a completely crystalline product was obtained, the total extract reaching 17% of the dry weight of bark. Through different solubilities in solvents three compounds *A*, *B*, and *C* have been isolated.

Compound *A*, $C_{27}H_{30}O_{14}$, m. p. 264·5° (decomp.), is, we consider, morindin, the water-soluble glycoside of morindone (1 : 5 : 6-trihydroxy-2-methylanthraquinone)—a constituent not isolated by Aston or Denz. The melting point is considerably higher than that previously recorded but varies considerably with the rate of heating. However, an authentic specimen had a similar melting point when taken at the same rate of heating (as the compound decomposes at its melting point any mixed melting point is without significance). A crystalline acetate and benzoate have been recorded for morindin but only amorphous derivatives were obtained in this case. The compound is a rhamnoglucoside of morindone since on hydrolysis with dilute acids it yields morindone and a mixture of sugars from which rhamnose was identified as its *p*-nitrophenylhydrazone and glucose as its osazone. The two sugars are probably present as a disaccharide attached to the β-hydroxy-group since methylation with excess of the reagent gave a product which still furnished morindone on hydrolysis (in the anthraquinone series α-hydroxyl groups are methylated with difficulty in contrast to β-hydroxyl groups which are readily methylated). All the earlier formulæ suggested for morindin do not agree with this rhamnoglucoside structure and should be abandoned. A curious property of this compound, hitherto unobserved, is that on boiling with water for a short time it is transformed into a water-insoluble isomeric form of almost identical melting point and rotation.

Compound *B*, $C_{15}H_{10}O_5$, m. p. 284·5°, has been identified as morindone by its melting point, colour reactions, and the preparation of the triacetate, tribenzoate, and mono- and tri-methyl ethers. A *dibenzoate* has also been prepared. This compound agrees with compound *A* of Aston. Morindone, in the free state or as its glycoside, morindin, also occurs naturally in *Morinda umbellata*, *M. citrifolia* and *M. tinctoria* (Klein, " Handbuch der Pflanzenanalyse ", 1932, Bd. III, p. 1034). The aglycone has been synthesised by Jacobsen and Adams (*J. Amer. Chem. Soc.*, 1925, **47**, 285) and by Bhattacharya and Simonsen (*J. Indian Inst. Sci.*, 1927, **10A**, 6).

Compound *C*, $C_{16}H_{12}O_4$, m. p. 302°, has been identified as rubiadin-1 methyl ether (3-hydroxy-1-methoxy-2-methylanthraquinone) by its melting point, colour reactions, and the

preparation of the dimethyl ether and acetate. A *benzoate* has also been prepared. This compound agrees with compound *B* of Aston and compound *A* of Denz despite the alleged conversion of the latter into alizarin. Rubiadin-1 methyl ether has already been found in the root bark of *citrifolia* (Simonsen, *J.*, **1920**, **117**, 561), *M. longiflora* (Barrowcliff and Tutin, *ibid.*, 1907, **91**, 1909), *C. areolata*, and *C. rubra* (forthcoming publications), its constitution following from its synthesis by Jones and Robertson (*ibid.*, 1930, 1699).

Although the three compounds can be separated fairly readily by fractional crystallisation this is more conveniently done in other ways. Morindin is easily obtained in crystalline form by extracting the air-dried bark with hot alcohol. Morindone and rubiadin-1 methyl ether are best obtained by acetone extraction of the air-dried bark from which the water-soluble morindin has first been removed by water soaking. Separation is then effected by taking advantage of the fact that by addition of calcium or barium hydroxide solution, morindone forms an insoluble purple salt and rubiadin-1 methyl ether a red soluble salt from which the free compounds are liberated on acidification.

In order to detect the number of coloured compounds in the bark an acetone solution was chromatographed on magnesium oxide and developed with the same solvent. Three distinct bands were formed, a top purple lake which could not be developed, a middle pinkish-red layer readily developed, and a bottom light-orange band which could be eluted with ease. On addition of dilute hydrochloric acid to the top band a red precipitate formed, identified after crystallisation as morindone. The bottom layer after complete elution and removal of the solvent yielded pure rubiadin-1 methyl ether, while extraction of the middle band with dioxan furnished morindin. No other bands could be detected. By chromatographing an acetone extract of the air-dried root bark the same three compounds were identified by a similar procedure.

The three constituents are present in the approximate proportion of morindin 40%, morindone and rubiadin-1 methyl ether each 30%. The presence of morindone and rubiadin-1 methyl ether together in the same plant contradicts the second empirical rule of Mitter and Biswas (*J. Indian Chem. Soc.*, 1928, **5**, 769) relating to the constitution of naturally occurring anthraquinone derivatives.

Morindone and morindin (after hydrolysis) are mordant dyes (cf. Oesterle and Tisza, *Arch. Pharm.*, 1907, **245**, 534; Perkin and Hummel, *loc. cit.*), and the phenomenonally high yield of dyes (cf. madder which contains 4% in the root bark) makes this tree extremely valuable to the home-dyer. Our dyeing results on wool, however, are somewhat different from those of Perkin and Hummel who used a partly purified extract of the root-bark of *M. umbellata*, containing morindone as the chief dye, and those of Oesterle and Tisza who used pure morindone on cotton-wool. Our experiments have led to rather lighter tones and are recorded in detail in the experimental section.

This is the first of a series of papers in which we hope to make a comprehensive survey of the *Coprosma* genus. The results may then also be of value in contributing to the problem of hybridisation which frequently occurs among members of this genus (cf. Allan, *Aust. New Zealand Ass. Adv. Sci.*, 1930, **20**, 429).

Experimental.

The cleaned, air-dried, finely broken bark was extracted exhaustively with alcohol in a Soxhlet. On cooling, orange-yellow needles (*A*) separated, followed after concentration by orange-red needles (*B*) and finally bright yellow needles (*C*). Alternatively, after removal of *A*, the mother liquors were taken to dryness under reduced pressure, and excess of calcium or barium hydroxide was added to the crystalline residue and warmed. Compound *C* forms a red soluble salt and *B* a purple insoluble salt with both reagents. The insoluble salt was collected and washed until the filtrate was colourless. The combined red filtrate was acidified, liberating *C* as yellow flocks, while *B* was liberated as orange-red flocks on treating a suspension of the insoluble salt with dilute hydrochloric acid. All three compounds were readily crystallised from glacial acetic acid.

Compounds *B* and *C* were more conveniently obtained by extracting water-soaked bark with acetone, distilling off the solvent, and working up with lime water as above.

Compound *A* is apparently identical with morindin. It forms long bright orange-yellow needles from glacial acetic acid, m. p. 264·5° (decomp.), $[\alpha]_D^{25°}$ — 90·9° (*l*, 1; *c*, 0·054 in dioxan) [Found (on air-dried material): C, 53·5, 53·4; H, 5·6, 5·7; loss on drying at 115°/vac., 3·82. Calc. for $C_{27}H_{30}O_{14}$, $1\frac{1}{2}$ H_2O: C, 53·55; H, 5·5; $1\frac{1}{2}$ H_2O, 4·5%]. The compound readily dissolves in cold water but, on boiling, a water-insoluble form, *β-morindin*, separated in long orange-yellow needles, m. p. 264° (decomp.), $[\alpha]_D^{25°}$ — 92·4° (*l*, 1; *c*, 0·055 in dioxan) (Found: C, 55·9, 56·4, 56·15; H, 5·3, 5·4, 5·4. $C_{27}H_{30}O_{14}$ requires C, 56·1; H, 5·2%). Both isomerides are completely soluble in dioxan, pyridine, acetone, and methyl alcohol, slightly soluble in ethyl alcohol and glacial acetic acid, and insoluble in ether, chloroform, benzene, and light petroleum. They give identical pinkish-red solutions with 10% sodium hydroxide solution, dilute ammonia, and concentrated sulphuric acid, the last solution changing to purple on standing, indicating hydrolysis to free morindone.

Hydrolysis of Morindin.—Morindin (735 mg.) was hydrolysed by heating with 2% sulphuric acid (75 c.c.) at 100° for 8 hours. After cooling, the amorphous precipitate crystallised from glacial acetic acid in needles, m. p. 284°, undepressed by pure morindone.

The filtrate from the hydrolysis was warmed and shaken with barium carbonate and the neutral liquid concentrated to a few c.c. During some weeks this deposited very large crystals, m. p. 87—88°, characteristic of rhamnose. The *p*-nitrophenylhydrazone, prepared from 100 mg. of the crystalline material, after recrystallisation from alcohol had m. p. 191·5° undepressed by an authentic specimen of rhamnose *p*-nitrophenylhydrazone.

A portion of the original sugar solution was treated with phenylhydrazine in the normal way. The crystalline product was repeatedly recrystallised from 60% alcohol, then dissolved in boiling acetone, and the solution concentrated to half volume and allowed to cool. The product after similar treatment with acetone had m. p. 204°, undepressed by authentic glucosazone.

Methylation of Morindin.—Morindin (105 mg.) dissolved in dry acetone (70 c.c.), anhydrous potassium carbonate (2 g.), and methyl sulphate (0·5 c.c.) were heated under reflux for 4 hours. The same quantities of potassium carbonate and methyl sulphate were again added and heating continued for another 4 hours. The red insoluble potassium salt was separated from the acetone layer, dissolved in water and hydrolysed with dilute sulphuric acid. Morindone was thus obtained (yield 15 mg.), m. p. 282° after crystallisation, undepressed by a pure specimen.

Compound *B* crystallises from glacial acetic acid in orange-red needles with a bronze lustre, m. p. 284·5°, and has been identified with morindone, for which Jacobsen and Adams (*loc. cit.*) record m. p. 281—282° but other workers somewhat lower values [Found: C, 66·6; H, 4·0; *M*(micro-Rast), 305. Calc. for $C_{15}H_{10}O_5$: C, 66·7; H, 3·7%; *M*, 270]. It is readily soluble in pyridine and acetone, slightly soluble in dioxan, ether, glacial acetic acid, and methyl and ethyl alcohol, and insoluble in water, benzene, light petroleum, and chloroform. It gives violet solutions with concentrated sulphuric acid and 10% sodium hydroxide solution.

The acetate, formed by heating morindone (30 mg.) with acetic anhydride (5 c.c.) and anhydrous sodium acetate (1·5 g.) for 2 hours, was repeatedly crystallised from glacial acetic acid and formed pale yellow needles, m. p. 259° (yield 25 mg., 57%). Jacobsen and Adams (*loc. cit.*) record m. p. 255—256·5° and other workers considerably lower values.

Both the mono- and the tri-methyl ether were obtained on methylation. A solution of morindone (134 mg.) in dry acetone (40 c.c.) and methyl sulphate (0·5 c.c.) was heated with dry potassium carbonate (2 g.) for 30 minutes. The dark-red insoluble material was filtered off and acidified with dilute hydrochloric acid. The yellow precipitate crystallised from glacial acetic acid (yield 50 mg., 40%) in orange-red needles, m. p. 256·5°, unchanged by further recrystallisation. Simonsen (*loc. cit.*) records m. p. 248° for the monomethyl ether. The yellow filtrate, after similar treatment with half the above reagents, was then poured into water (100 c.c.). The dark-yellow oil formed crystallised from glacial acetic acid in characteristic fox-tail-like aggregates, m. p. 226° (yield, 27 mg., 16%). Simonsen (*loc. cit.*) gives m. p. 229° for the trimethyl ether.

The tribenzoate was formed by allowing a mixture of morindone (100 mg.), pyridine (4 c.c.), and benzoyl chloride (2 c.c.) to stand overnight. After being warmed for 10 minutes the solution was poured into water, the viscid oil produced solidifying on trituration with alcohol. After crystallisation from glacial acetic acid it formed light-yellow plates, m. p. 234° (yield 140 mg., 70%). Jacobsen and Adams (*loc. cit.*) record m. p. 233—234° and Simonsen (*loc. cit.*) m. p. 218—219°, for the tribenzoate.

A *dibenzoate* was prepared by warming a solution of morindone (108 mg.) in pyridine (3 c.c.) and benzoyl chloride (1 c.c.) for a few minutes, and pouring into water (200 c.c.). The coloured oil formed was washed with 5% sodium carbonate solution and then crystallised from glacial acetic acid to form bright orange-yellow prisms, m. p. 206·5°, unchanged by further recrystallisation (yield 131 mg., 68%) (Found: C, 72·85, 73·0; H, 3·9, 4·2. $C_{29}H_{18}O_7$ requires C, 72·8; H, 3·8%). This is probably the 2 : 5-derivative.

Compound *C*, bright-yellow needles or plates from glacial acetic acid, m. p. 302°, has been identified with rubiadin-1 methyl ether [Found: C, 71·7, 71·5, 71·6; H, 4·8, 4·7, 4·3; *M*(micro-Rast), 240. Calc. for $C_{16}H_{12}O_4$: C, 71·6; H, 4·5%; *M*, 268]. The m. p. is *ca.* 10° higher than that recorded by other workers [cf. Barrowcliff and Tutin (*loc. cit.*), Simonsen (*loc. cit.*), and Jones and Robertson (*loc. cit.*)]. Rubiadin-1 methyl ether is freely soluble in acetone, pyridine, and dioxan, slightly soluble in ether, glacial acetic acid, toluene, and methyl and ethyl alcohol, and insoluble in water, benzene, chloroform, and light petroleum. It gives orange-red solutions with concentrated sulphuric acid and sodium hydroxide solution.

The acetate, prepared by heating rubiadin-1 methyl ether (90 mg.) with acetic anhydride (1 c.c.) and anhydrous sodium acetate (100 mg.) for 2 hours and pouring into water (200 c.c.), crystallised from ethyl acetate in long lemon-yellow prisms, m. p. 183° (yield 90 mg., 75%) unchanged by further recrystallisation. Barrowcliff and Tutin (*loc. cit.*) record m. p. 173°, and Simonsen (*loc. cit.*) and Jones and Robertson (*loc. cit.*) m. p. 174°.

Rubiadin dimethyl ether was prepared by heating a solution of rubiadin-1 methyl ether (90 mg.) in dry acetone (40 c.c.) and methyl sulphate (1 c.c.) with dry potassium carbonate (2 g.) for ½ hour. The acetone layer was then poured into water (50 c.c.); the crystalline product (yield 80 mg., 86%) recrystallised from alcohol in pale yellow needles, m. p. 161° (Found: C, 72·7; H, 5·3. Calc. for $C_{17}H_{14}O_4$: C, 72·3; H, 4·9%). Barrowcliff and Tutin (*loc. cit.*) reported m. p. 181° for this derivative, a result queried by Jones and Robertson (*loc. cit.*) who obtained m. p. 158°.

The *benzoate* was obtained by heating a solution of rubiadin-1 methyl ether (197 mg.) in pyridine (5 c.c.) and benzoyl chloride (1 c.c.) for a few minutes and then pouring into water (200 c.c.). The dark yellow oil produced after treatment with 5% sodium carbonate solution crystallised from glacial acetic acid in yellow orthorhombic prisms (yield 120 mg., 45%), m. p. 160° (Found: C, 74·0; H, 4·3. $C_{23}H_{16}O_5$ requires C, 74·2; H, 4·3%).

Chromatographic Separation.—Preliminary experiments with a number of adsorbents showed that

magnesium oxide was the most suitable. A clear acetone extract was added to a series of columns (8 ins. × ½ in.) of this absorbent and developed with the same solvent. The top purple band was washed with acetone until a clear band separated it from the next. The purple lake was then suspended in water and acidified with dilute hydrochloric acid. The red flocculent precipitate was collected, well washed with water, and crystallised from glacial acetic acid to form orange-red needles, m. p. 284°, undepressed by pure morindone. The bottom light-pink band was eluted completely with acetone; the yellow solution on concentration yielded bright yellow needles, m. p. 302°, undepressed by pure rubiadin-1 methyl ether. The central light-orange band was extruded and extracted with boiling dioxan. After concentration of the extract under reduced pressure water-soluble orange needles separated, m. p. 260° (decomp.), identified with morindin by its m. p. and colour reactions.

Dyeing Properties of Morindone.—The dye was applied in aqueous solution containing 25% acetone–alcohol to mordanted wool with the following results. Iron (ferric), brownish-black; copper, purplish; potassium dichromate, aluminium, reddish purple; uranium, very dark green; lead, nickel, lilac tones; tin, bright-red; molybdenum, titanium, bismuth, reddish tones; zinc, zirconium, light chocolate; cadmium, light brown; manganese, fawn.

The analyses are by J. Mills, Adelaide University, Drs. Weiler and Strauss, Oxford, and R. N. Seelye of this Department.

We are indebted to the Chemical Society, the Royal Society of New Zealand, and the Department of Scientific and Industrial Research, New Zealand, for grants, to Imperial Chemical Industries Ltd. for gifts of chemicals, and to Dr. Cross for anthraquinone derivatives and an authentic specimen of morindin from the collection of colouring matters of the late Professor A. G. Perkin.

AUCKLAND UNIVERSITY COLLEGE, NEW ZEALAND. [*Received, May 14th*, 1947.]

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117. *Chemistry of the* Coprosma *Genus. Part II. The Colouring Matters from* Coprosma areolata.

By LINDSAY H. BRIGGS, (MISS) MARGOT R. CRAW, and JACK C. DACRE.

The bark of *Coprosma areolata* is shown to contain the phenomenally high yield of 23% of two anthraquinone derivatives, rubiadin-1 methyl ether and a new compound, *areolatin*, $C_{15}H_{10}O_6$, which is probably 1 : 5 : 6 : 7-tetrahydroxy-2-methylanthraquinone.

Coprosma areolata is a shrub or small tree 6—15 feet high, endemic to New Zealand and occurring commonly in lowland forests throughout the North and the South Island. A preliminary investigation was made by Aston (*New Zealand J. Sci. Tech.*, 1918, **1**, 264, 346) who observed that the deep brown inner bark gave a violet coloration with sodium hydroxide solution and dyed wool either as a substantive dye or with mordants. No attempt was made to isolate the dye.

An exhaustive acetone extract of the air-dried bark when subjected to chromatographic adsorption on a magnesium oxide column produced a bluish-black lake and a light-orange band readily eluted with acetone. Removal of the solvent used to elute this band furnished rubiadin-1 methyl ether, characterised by its melting point, colour reactions, and preparations of its acetate, benzoate and methyl ether. This compound has already been isolated from *C. australis* (Part I, previous paper) and *C. rubra* (forthcoming publication).

Acidification of the lake produced a brownish-red water-insoluble product crystallising from glacial acetic acid in needles or plates which shrink at 298° without melting and gradually carbonise above this temperature. Analyses agreed with the formula $C_{15}H_{10}O_6$, and the colour reactions and its derivatives indicated that it is a new compound for which the name *areolatin* is proposed.

The two compounds can be obtained in quantity by extraction with acetone, removal of solvent, and treatment with calcium or barium hydroxide solution, rubiadin-1 methyl ether forming a red soluble calcium or barium salt, and areolatin, blackish insoluble salts from which the colouring matters can be recovered by acidification.

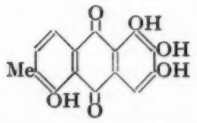
By using the chromatographic procedure, the same two colouring matters were separated from the root-bark but in considerably less yield. In both cases the compounds are present in approximately equal amount.

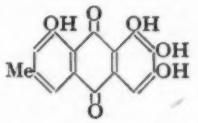
Areolatin gives colour reactions typical of anthraquinones, and its reduction product with hydriodic acid the reactions of an anthranol. It forms a tetra-acetate and a tetrabenzoate, and must therefore contain four hydroxyl groups. Since it forms a tetramethyl ether, all four groups must be phenolic. It furnishes one molecule of acetic acid in the Kuhn–Roth oxidation with chromic acid, and the methyl group thus indicated is in β-position, since zinc dust distillation produced β-methylanthracene. At least one phenolic group is adjacent to the methyl group, since the tetra-acetate could not be converted into the corresponding carboxylic acid by oxidation with chromic acid (cf. Anslow and Raistrick, *Biochem. J.*, 1940, **34**, 1124). Areolatin

is a strong mordant dye, indicative of phenolic groups in 1 : 2-position, while 1 : 4-groups are absent as shown by lack of fluorescence in acetic acid solution (Raistrick, Robinson, and Todd, *ibid.*, **1934**, **28**, 559). The absorption spectra in alcoholic and concentrated sulphuric acid solutions indicated a relationship to both morindone and anthragallol, while the colours produced on mordanted wool were almost indistinguishable from those of anthragallol. The presence of two phenolic groups in β-positions was indicated by the isolation of a dimethyl ether as a by-product in the methylation to the tetramethyl ether, while the constitution of the other half of the molecule was confirmed by the isolation (in small yield) of 3-methoxy-4-methylphthalic anhydride on oxidation of the tetramethyl ether with chromic acid.

From these facts it appeared that areolatin is 1 : 5 : 6 : 7-tetrahydroxy-2-methylanthraquinone (I). A 1 : 8-structure (II) is not rigidly excluded, but is less likely on spectrochemical

(I.)





(II.)

as well as phytochemical evidence, since there are no records of 1 : 8-compounds in the *Rubiaceæ* although they occur in the *Rhamnaceæ* and the lower plants. A final decision will be attempted by synthesis.

This is the first record of an anthraquinone with four phenolic groups occurring in the higher plants, although two, cynodontin (Raistrick, Robinson, and Todd, *loc. cit.*) and catenarin (Anslow and Raistrick, *ibid.*, **1941**, **35**, 1006), occur in species of moulds. This fact and the occurrence of rubiadin-1 methyl ether and areolatin together in the same plant are further exceptions to the empirical rules of Mitter and Biswas (*J. Indian Chem. Soc.*, **1928**, **5**, 769) proposed for natural anthraquinones.

Experimental.

We are indebted to the Auckland City Council for their permission to collect the bark used in this investigation from mature trees at Smith's Bush near Auckland.

The finely broken air-dried bark was exhaustively extracted with acetone. On concentration, a completely crystalline mixture of lemon-yellow needles and dark-red plates separated. For chromatographic adsorption, however, a complete acetone solution was employed and adsorbed on a magnesium oxide column, 8 in. × ½ in. A bluish-black lake formed on the top of the column followed by a light-orange band. Development of the column with acetone failed to affect the lake but removed the lower band completely. Removal of the solvent afforded bright yellow needles, m. p. 302°, identified by m. p. and mixed m. p. with rubiadin-1 methyl ether. This was confirmed by the preparation of the acetate, m. p. 174°, methyl ether, m. p. 159°, and benzoate, m. p. 159·5° (for details see Part I, *loc. cit.*), all undepressed by authentic specimens.

The black lake was extruded, suspended in water, and decomposed with dilute hydrochloric acid. The dark-red precipitate, after crystallisation from glacial acetic acid, formed plates or needles of *areolatin* which shrank at 298° without melting and gradually carbonised above this temperature. Further recrystallisation from glacial acetic acid or alcohol did not change this characteristic shrinking point (Found : C, 62·9, 63·3; H, 3·8, 3·6. $C_{15}H_{10}O_6$ requires C, 62·9; H, 3·5%). The *C*-Me value was determined by the Kuhn–Roth method as modified by Barthel and La Forge [*Ind. Eng. Chem.* (*Anal.*), **1944**, **16**, 434] (Found : *C*-Me 6·1. $C_{15}H_{10}O_6$ requires for 1 *C*-Me, 6·1%).

The two compounds could be conveniently obtained in quantity by treating the material obtained by acetone extraction with dilute ammonia solution followed by excess of calcium hydroxide solution. The black insoluble calcium salt of areolatin was washed free from the red soluble salt of rubiadin-1 methyl ether, and the free compounds were regenerated by acidification.

Areolatin is readily soluble in acetone, dioxan, and pyridine, less soluble in alcohol, glacial acetic acid, ethyl acetate, and ether, difficultly soluble in methyl alcohol, and insoluble in water, chloroform, and hydrocarbon solvents. With concentrated sulphuric acid it gives a dark reddish-purple coloration deepening to purple on addition of boric acid. Dilute sodium hydroxide solution gives a reddish solution changing quickly to reddish-brown. It is insoluble in sodium carbonate but dissolves in dilute ammonia solution to a brown solution changing quickly to greenish-blue. In concentrated nitric acid it is insoluble in the cold but dissolves on warming with a cherry-red–orange yellow–orange-brown coloration. The calcium, barium, and magnesium salts are purplish-black.

Areolatin Tetra-acetate.—Areolatin (85 mg.) was heated under reflux for 2 hours with acetic anhydride (5 c.c.) and fused sodium acetate (500 mg.). The hot solution was poured into water (100 c.c.) and the yellow precipitate repeatedly crystallised from glacial acetic acid to give long light-yellow needles of the *acetate* (yield 80 mg., 60%), m. p. 238° (Found : C, 60·5, 60·7; H, 4·0, 4·1. $C_{23}H_{18}O_{10}$ requires C, 60·8; H, 4·0%).

Areolatin Tribenzoate.—Areolatin (72 mg.), pyridine (3 c.c.), and benzoyl chloride (1 c.c.) were warmed for a few minutes and poured into ice-cold water (100 c.c.). The reddish-black sticky oil produced was separated by decantation, washed with 5% sodium carbonate solution, and dried. The *tribenzoate* then separated from glacial acetic acid in short, thick, orange-yellow crystals (yield 63 mg., 42%), m. p. 220°, unchanged on further recrystallisation (Found : C, 72·1, 71·8; H, 3·7, 3·9. $C_{36}H_{22}O_9$ requires C, 72·2; H, 3·7%).

Areolatin Tetrabenzoate.—Areolatin (140 mg.), pyridine (4 c.c.), and benzoyl chloride (2 c.c.) were shaken and allowed to stand overnight. Then, after being warmed for 10 minutes, the mixture was poured into ice-cold water (100 c.c.). The reddish-black oil formed solidified on trituration with hot alcohol, and after repeated crystallisation from glacial acetic acid the *tetrabenzoate* formed very pale greenish-yellow diamond-shaped plates, m. p. 281° (Found: C, 73·4, H, 3·7. $C_{43}H_{26}O_{10}$ requires C, 73·5; H, 3·7%).

Methylation of Areolatin.—Areolatin (210 mg.) dissolved in dry acetone (25 c.c.), anhydrous potassium carbonate (4 g.), and methyl sulphate (2 c.c.) were heated under reflux for 1 hour. Further potassium carbonate (2 g.) and methyl sulphate (1 c.c.) were added, and heating was continued for 8 hours. The yellow acetone solution was decanted and poured into ice–water. The yellow needles of *areolatin tetramethyl ether*, which separated immediatley (yield, 240 mg., 95%), after recrystallisation from glacial acetic acid had m. p. 175° (Found: C, 66·6; H, 5·4; OMe, 34·3. $C_{19}H_{18}O_6$ requires C, 66·7; H, 5·2; 4OMe, 36·2%).

The *dimethyl ether* could be obtained as a by-product by working up the red potassium salt from the above experiment, but was preferably prepared under milder conditions. Areolatin (250 mg.) dissolved in dry acetone (30 c.c.), anhydrous potassium carbonate (4 g.), and methyl sulphate (2 c.c.) were heated under reflux for ½ hour. The dark red salt was separated from the acetone, suspended in water, and acidified with dilute hydrochloric acid. The orange-yellow precipitate after repeated crystallisation from glacial acetic acid (yield 100 mg., 40%) formed plates, m. p. 220° (Found: C, 65·2; H, 4·4; OMe, 18·2. $C_{17}H_{14}O_6$ requires C, 65·0; H, 4·4; 2OMe, 19·7%). The dimethyl ether failed to dye wool mordanted with potash alum or stannous chloride.

Reduction of Areolatin.—A 1 : 20 mixture of areolatin (200 mg.) and zinc dust was heated in a stream of hydrogen. The bright yellow product (yield 20 mg., 15%) which sublimed in the cooler part of the tube, was repeatedly recrystallised from alcohol, and then formed almost colourless leaflets or plates, m. p. 203°, undepressed by pure β-methylanthracene, for an authentic sample of which we are indebted to Dr. Siegfried, Zofingen.

Areolatin (464 mg.) dissolved in glacial acetic acid (10 c.c.), hydriodic acid (2·5 c.c., *d* 1·35), and red phosphorus (500 mg.) were heated under reflux for 4 hours. On cooling, the mixture was poured into water (200 c.c.), giving a greenish-black precipitate and a reddish-brown solution which was decolorised by the addition of a slight excess of sodium hydrogen sulphite solution. A portion of the solid material on sublimation at 180°/0·005 mm. formed yellow plates, m. p. 229°, which were insufficient for further characterisation but gave the characteristic tests for an anthranol.

Oxidation of Areolatin Tetramethyl Ether.—A solution of the tetramethyl ether (2·5 g.) in acetic anhydride (25 c.c.) and glacial acetic acid (15 c.c.) was heated to 100° and vigorously stirred during ½ hour while chromic acid (6 g.) dissolved in glacial acetic acid (25 c.c.) and water (4 c.c.) was added. The solution was then reduced to *ca.* 10 c.c. under reduced pressure and extracted with ether (8 × 25 c.c.) which on evaporation yielded long white needles (20 mg.). These crystallised in the same form from toluene, m. p. 134—135°, and had the same m. p. and solubilities as those recorded for 3-methoxy-4-methylphthalic anhydride (Simonsen and Rau, *J.*, 1921, 1345). The analysis, although not good, did not agree with any other possible structure derivable from a tetramethoxymethylanthraquinone (Found: C, 63·1; H, 5·4. Calc. for $C_{16}H_8O_4$: C, 62·5; H, 4·2%).

Absorption Spectra.—The absorption spectra of the undermentioned compounds were measured in the visible region using a Coleman model II Universal Spectrophotometer. We are indebted to Dr. W. Gilmour of the Auckland Public Hospital for permission to use this instrument and to Mr. J. B. Brown for assistance in the measurements. The analytically pure compounds were measured in alcohol, concentrated sulphuric acid, and, where possible, N/20-sodium hydroxide solution.

	Alcohol.		Sulphuric acid.		N/20-Sodium hydroxide.	
	log ε.	λ, A.	log ε.	λ, A.	log ε.	λ, A.
Areolatin	4·438	4375	4·751	5480	—	—
	3·842	5610	4·026	7020	—	—
Morindone	4·425	4540	4·711	5610	4·508	5450
	4·218	5510	—	—	—	—
Anthragallol	4·258	4210	4·481	4780	—	—
	—	—	3·606	7040	—	—
Morindin	4·171	4425	4·373	5620	4·158	5020
β-Morindin	4·208	4430	—	—	4·193	5010
Rubiadin-1 methyl ether	3·616	3980	4·452	4560	4·175	4710
	2·820	5050	—	—	—	—
Rubiadin dimethyl ether	—	—	4·432	4590	—	—

Dyeing Properties of Areolatin.—The colours produced by areolatin on wools mordanted with the following compounds are practically indistinguishable from those of anthragallol. Iron, uranium, blackish-brown; tin, reddish brown; bismuth, molybdenum, rich brown; chromium, titanium, brown; strontium, cadmium, brownish-yellow; boron, nickel, zinc, manganese, tungsten, chrome alum, dull yellow; zirconium, dull yellowish-brown; lead, copper, dark fawn; aluminium, light fawn.

The analyses are by J. Mills, University of Adelaide, Drs. Weiler and Strauss, Oxford, and R. N. Seelye of this Department.

We are indebted to the Chemical Society, the Department of Scientific and Industrial Research, New Zealand, and the Royal Society of New Zealand for grants, and to Imperial Chemical Industries Ltd. for gifts of chemicals.

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118. *The Structure of Molecular Compounds. Part V. The Clathrate Compound of Quinol and Methanol.*

By D. E. Palin and H. M. Powell.

The substance formerly described as β-quinol is shown by chemical analysis, by molecular-weight determination from unit cell dimensions, and by detailed crystal structure determination to be a compound $3C_6H_4(OH)_2,CH_3{\cdot}OH$. The structure, similar to that of the corresponding compound of quinol with sulphur dioxide, consists of two interpenetrating giant molecules of hydrogen-bonded quinol units. The methanol molecules are imprisoned in cavities between the two giant molecules. They are arranged with their long axes parallel to the *c* direction of the hexagonal axes and the structure is thus non-centrosymmetric.

On crystallisation from water, ethanol, or ether, quinol forms needle-like hexagonal crystals, but when methanol is used as solvent stout hexagonal prisms with rhombohedron terminations are obtained. The crystals formed in these two cases are morphologically different although it is not clear whether this was observed by early crystallographers. Groth (*Ber.*, 1868, **1**, 164) stressed the needle character of the crystals obtained from water, but the interfacial angles that he gives are similar to those of Heydrich (*Z. Krist.*, 1911, **48**, 260), who carried out his measurements on crystals grown from methanol and are in agreement with those reported below. The two forms obtained from water and methanol were, however, clearly distinguished by Caspari (*J.*, 1926, 2944; 1927, 1093), who called them α- and β-quinol respectively. He gave for α-quinol the unit cell dimensions $c = 5{\cdot}62$, $a = 22{\cdot}08$ A., space-group C_{3i}^1 with 18 molecules per unit cell. For β-quinol he found $c = 5{\cdot}53$, $a = 16{\cdot}25$ A. with 9 molecules per unit cell. He found dissimilar terminal faces $\{10\bar{1}1\}$ and $\{20\bar{2}\bar{3}\}$ for the ends of the crystals and gave the space-group as C_3^1.

During the early stages of the crystal-structure analysis of the compound 3 quinol : SO_2 (Part III, *J.*, 1947, 208) it was noted that in cell dimensions, certain morphological characteristics, and general pattern of *X*-ray diffraction effects there was a strong similarity between this compound and " β-quinol " as described by Caspari, and *X*-ray photographs were made of both with a view to their possible use for deducing signs of the structure factors from the differences in the two sets of intensities. For " β-quinol " the space-group found was $R3 - C_3^4$, not C_3^1 as proposed by Caspari. Moreover, the observed *a* dimension, $16{\cdot}5_6\ kX$, differed appreciably from that given by Caspari, and consequently the weight of the unit cell was greater than that corresponding to 9 molecules of quinol. In view of this complication and a confirmation by a positive pyroelectric test of the hemimorphism reported by Caspari (which is not found for the sulphur dioxide compound), the structure given in Part III was obtained by other methods. From the results of this determination and an examination of other similar compounds (to be described in Part VI) it seemed clear that all the compounds in this series had a similar structure of two interpenetrating giant molecules of hydrogen-bonded quinol enclosing the sulphur dioxide or other molecule. It seemed impossible to account for the non-centrosymmetric character of the crystals obtained from methanol if they consisted of the quinol structure only. The observed structure-factor values also were such that it appeared certain that they must give a noticeable electron density in the region corresponding to the sulphur dioxide or other molecule. These observations, combined with the knowledge of the excess weight of the unit cell, led to the view that the crystals were not those of a modification of pure quinol but that they contained a second component. The most likely added molecule was methanol, although there was a possibility that water might also be present if the solvent used was not anhydrous.

It was next proved that the compound could be obtained from pure anhydrous methanol, and confirmation of the presence of methanol in the crystalline compound was obtained by dissolving a quantity of it in water and distilling in an all-glass apparatus. Distillation started at 99° and the distillate, which smelt of methanol, had a specific gravity less than 1·00. There may have been some distillation in steam of quinol, and an accurate estimate from the specific gravity of the concentration of methanol in the original material could not be expected. Analyses showed the composition of the *compound* to be approximately 3 quinol : MeOH.

Since the quinol part of the structure is evidently very nearly the same as that in the centrosymmetric sulphur dioxide compound, the non-centrosymmetric character must arise from the methanol molecules. It seemed likely therefore that these molecules were oriented with their lengths parallel to the *c* axis, and from a consideration of the state of the sulphur dioxide molecule in the corresponding structure it seemed probable that the methanol molecule would be free to undergo considerable motion in the neighbourhood of the axis. If this general arrangement

is correct, it is readily seen that, although the structure as a whole is polar and conforms to the space-group $R3$, a projection of the structure on the c face would be centrosymmetric and the corresponding Fourier summation of electron density could be carried out by use of the experimental F_{hk0} values with a positive or negative sign as required.

In the ideal case, where the only difference between two structures lies in the electron weight of the scattering unit at a symmetry centre, any changes in reflexion intensity must be due to change in positive contribution of this unit as, *e.g.*, in the phthalocyanines (Robertson, *J.*, 1935, 615; 1936, 1195; Robertson and Woodward, *J.*, 1937, 219). The signs of the stronger reflexions or of those which are absent in one case or the other may be determined unequivocally, but for the weaker reflexions it is difficult to be certain whether or not a sign reversal has occurred. In the present case, however, the position is further complicated by the small changes in atomic parameters for the quinol molecules to be expected in consequence of the differences in cell dimensions, and by the fact that the scattering unit at the origin can only be considered to be distributed about this point in some way. Since, however, the signs for the F_{hk0} terms in the sulphur dioxide compound had already been computed, it was possible to allot signs to the methanol compound terms as follows. The structure-factor values for the two compounds, reduced to a similar scale, were tabulated together with the signs previously derived for the sulphur dioxide compound. Signs for the methanol compound were allotted on the assumption that the changes in magnitude are due to the decrease in positive contribution of the scatterer at the origin in the methanol compound and that they are influenced to only a minor extent by changes in the quinol co-ordinates. These results are shown in Table I. In general, structure factors which are positive for the sulphur dioxide compound are decreased in magnitude for the methanol compound, and for negative structure factors the converse is true. In the same way, except for $F_{16\,1\,\overline{17}\,0}$, spectra which are absent in the methanol compound have weak positive values in the sulphur dioxide compound, and this justifies the allocation of negative signs to those which were observed for the methanol compound but not for the sulphur dioxide compound. The structure factors which do not comply with the above generalisations are indicated in the table. Except for $F_{7\,4\,\overline{11}\,0}$ there appears to be little doubt about the correctness of the sign

TABLE I.

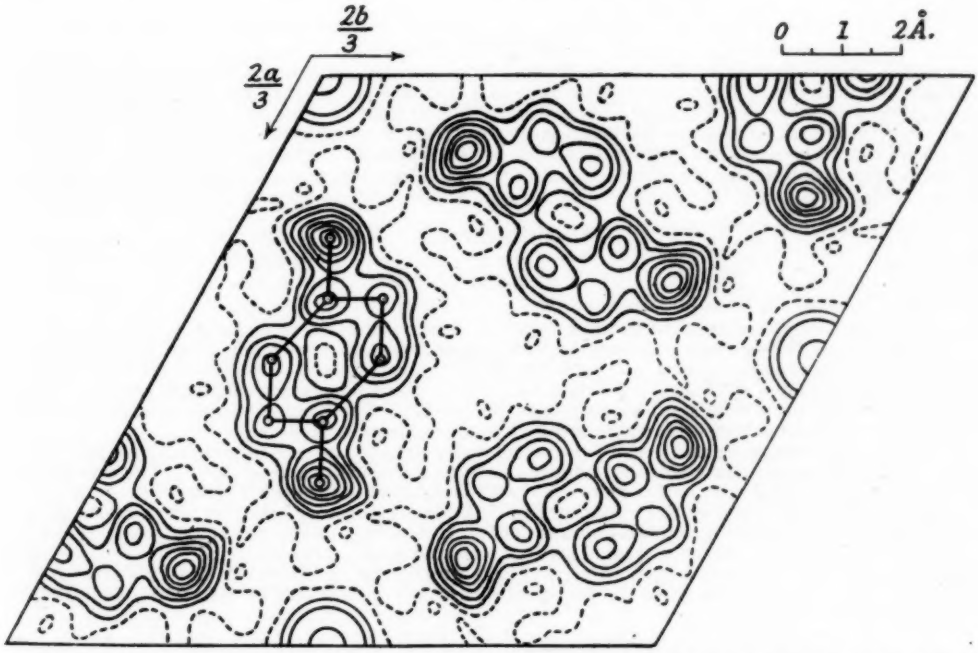
Allocation of signs for F_{hk0}.

Indices	SO_2 compound.		MeOH compound.		Indices	SO_2 compound.		MeOH compound.	
hk.	F.	Sign.	F.	Sign deduced.	*hk.*	F.	Sign.	F.	Sign deduced.
0 3	44	—	66	—	5 2	58	+	45	+
0 6	28	—	45	—	5 5	8	+	*a*	*a*
0 9	48	+	42	+	7 1	21	+	*a*	*a*
0 15	9	+	13	+ *	7 4	12	+	23	— *
1 1	28	—	15	— *	7 7	39	+	42	+
1 4	70	+	46	+	7 10	17	—	15	— *
1 7	13	—	23	—	8 2	27	—	36	—
1 13	17	—	18	—	8 11	13	+	12	+
2 2	86	+	69	+	9 9	*a*	*a*	11	—
2 5	57	+	48	+	10 1	37	+	35	+
2 8	22	—	29	—	10 4	17	—	15	— *
2 11	10	+	15	+ *	10 7	21	—	15	— *
3 3	90	+	76	+	11 2	17	+	18	+
3 6	23	+	14	+	11 8	*a*	*a*	12	—
3 9	14	+	15	+	12 3	14	—	18	—
3 12	17	—	15	—	13 1	22	—	18	—
4 1	35	—	46	—	13 4	15	+	13	+
4 4	34	+	26	+	16 1	11	—	*a*	*a*
4 13	*a* †	*a* †	12	—					

* The structure factors marked * do not conform to the generalisations mentioned in the text.
† *a* denotes "absent."

given, on account of the decisive nature of the calculated sign for the sulphur dioxide compound. For $F_{7\,4\,\overline{11}\,0}$ an increase in magnitude for the methanol compound was observed and since the calculated positive value for the sulphur dioxide was not sufficiently high to be conclusive, it was decided to take the sign as a negative in the methanol compound. It will be seen that the maximum number of negative signs has been allotted, so that any electron density shown at the origin in the projection provides certain proof of the presence of scattering matter near this point.

The electron-density plot is shown in the figure. It is very similar in general appearance to the corresponding projection for the sulphur dioxide compound (Fig. 6, Part III, *loc. cit.*), but with a much reduced peak at the origin. The oxygen atoms of the quinol molecules are seen grouped in hydrogen-bonded hexagons around the symmetry axes. The side of the hexagon is $2{\cdot}7_1$ A. with little change from that in the sulphur dioxide compound, but since the projected length oxygen–oxygen in the same quinol molecule has increased from $3{\cdot}9_5$ to $4{\cdot}1_2$ A. there must be a corresponding decrease in the angle of tilt of this oxygen–oxygen axis to the plane of the projection. The angle, 45° in the sulphur dioxide compound, decreases to about $41\frac{1}{2}°$. This change of tilt, which is related to the alterations in cell dimensions, is discussed further in Part VI in relation to other structures in this same series. It was assumed that the quinol molecule



Relative electron density projected on (0001). *The atomic centres are indicated for one quinol molecule.*

would have the same shape and dimensions as determined in Part III, and on the basis of this and the electron-density projection the atomic parameters of Table II were estimated.

TABLE II.

Atom.	x.	y.	Atom.	x.	y.
Quinol oxygen	$0{\cdot}19_0$	$0{\cdot}10_0$	Carbon C_2	$0{\cdot}33_0$	$0{\cdot}11_0$
Carbon C_1	$0{\cdot}26_1$	$0{\cdot}13_1$	,, C_3	$0{\cdot}26_1$	$0{\cdot}18_0$

From the good resolution, compatibility with required molecular dimensions, and absence of unwanted peaks in the projection it seems unlikely that there can be serious errors in the $F_{A\bar{h}0}$ terms or their signs, and it is therefore necessary to consider the heights of the various peaks. For the oxygen atom and carbon atoms C_1,C_2,C_3 these heights in arbitrary units above an estimated zero are 38, 29, 26, and 23. With allowance for the hydrogen atoms associated with each atom the corresponding electron weights, commonly observed to give a rough parallelism with these heights, are 9, 6, 7, 7. The oxygen and C_1 peaks are in about the expected ratio, but C_2 and C_3 are distinctly lower than C_1 whereas they might be expected to be higher. The peaks are affected in different ways by their neighbours but the effect seems to be real: it was also noticed for the sulphur dioxide compound in the projection which is derived from an independent set of observed $F_{A\bar{h}0}$ magnitudes. It may be explained by the oscillation of the quinol molecule about its oxygen–oxygen axis. This leaves the atomic centres of the C_1 atoms and of the oxygen, which is fairly firmly held at both ends through hydrogen bonds, in

their original positions but displaces the centres of C_2 and C_3 with a consequent broadening and lowering of the electron-density peaks.

The peak at the origin has a height of 21 (on the same arbitrary scale), slightly less than that of C_3 and much smaller than would be expected for a methanol molecule if it were fixed with its carbon–oxygen line on the *c* axis. It is also a rather flat peak, and it seems probable that these effects arise from considerable movement of the methanol molecule in its enclosing cavity, when the electron density that should correspond to it tends to become lost in the surrounding background. That there could be such motion is known from the nature of the enclosure and from observations on the sulphur dioxide in its similar cavity. It provides further evidence that the relationship of the two molecular species in these molecular compounds is that of enclosure of one in a cagework of the other rather than that of any union by chemical bonds.

Experimental.

Crystals were obtained by slow crystallisation from a saturated solution of quinol in methanol at ordinary temperatures. They were in the form of hexagonal prisms with rhombohedral terminations which in most crystals were the same at both ends although some crystals appeared to be hemimorphic. They were fairly hard, showed no marked cleavage, and had weak negative birefringence. The density (flotation) was $1{\cdot}35_{0\pm5}$. Tests for pyroelectricity by the liquid-air method gave a weak positive result. Morphological data obtained by Miss M. W. Porter, Mineralogy Department, Oxford, on crystals which showed {10$\bar{1}$}, {100} and {11$\bar{1}$} (rhombohedral indices) are compared with previously reported values:

	Heydrich (*loc. cit.*).	Groth (*loc. cit.*).	M. W. Porter.
(100) : (10$\bar{1}$)	58° 4′	58° 22′	58° 13′
c : *a*	0·668	—	0·664

The axial ratio here given corresponds to $2c : a$ for the unit cell derived from *X*-ray examination.

Oscillation and Weissenberg photographs with copper radiation were taken about the same axes as for the sulphur dioxide compound, and structure-factor values derived in a similar manner. The cell dimensions found were $a = 16{\cdot}5_{8\pm3}$, $c = 5{\cdot}5_{5\pm2}$ *kX*. The *c* dimension agrees with that given by Caspari (*loc. cit.*) but that for *a* differs appreciably from his (16·25). The present values give $2c : a = 0{\cdot}671$, more nearly in agreement with the value deduced from crystal measurement.

From the cell dimensions and density the calculated weight of the cell, in molecular weight units, is 1078. This value is 88 in excess of that required for nine molecules of quinol (990). The excess is well outside the experimental error and is compatible with that required for 3MeOH (96).

Analysis of two samples, by F. P. Johnson, I.C.I. Widnes laboratory, gave: C, 63·4, 63·5; H, 5·95, 6·1; $H_2O < 0{\cdot}5$. [$3C_6H_4(OH)_2{,}CH_3{\cdot}OH$ requires C, 63·0; H, 6·07%. Calc. for quinol: C, 65·4; H, 5·45%]. A separate determination of the methanol content was also made. The methanol was separated from quinol by azeotropic distillation with water, and isothermally distilled from this distillate into excess of acid dichromate; back titration of the excess of dichromate gave: MeOH, 8·6 [$3C_6H_4(OH)_2{,}CH_3{\cdot}OH$ requires $CH_3{\cdot}OH$, 8·85%].

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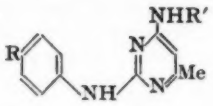
119. *Synthetic Antimalarials. Part XXIII. 2-Arylguanidino-4-aminoalkylaminopyrimidines. Further Variations.*

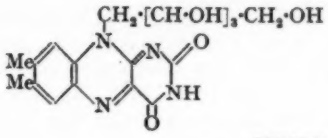
By W. H. Cliffe, F. H. S. Curd, F. L. Rose, and (Miss) M. Scott.

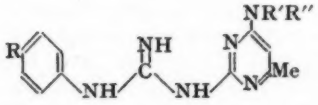
Curd and Rose (Part IV, *J.*, 1946, 362) described a series of 2-phenylguanidino-4-dialkylaminoalkylamino-6-methylpyrimidines, many of which showed antimalarial activity when tested against *P. gallinaceum* in chicks. The present work concerns further syntheses of the same type with variations of the substituent in the aryl group and the complexity of the basic side chain, and introduction of substituents into position 5 of the pyrimidine ring as well as different groups in position 6. No notable increase in therapeutic activity is recorded.

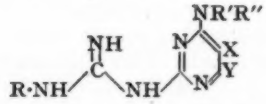
Anilinopyrimidines of type (I; R = Cl, R′ = dialkylaminoalkyl) have been widely varied in attempts to enhance the antimalarial activity exhibited by some members of the series (Part I, *J.*, 1946, 343; Part II, *ibid.*, p. 351; Part V, *ibid.*, p. 366; Part VII, *ibid.*, p. 378). These variations have included not only a routine investigation of the influence of changing the nature and position of the aromatic subsitiuent and the size of the basic side-chain group, but have sought also to promote increased therapeutic activity by effecting such substitution in the benzene and pyrimidine rings (mainly appropriately placed methyl groups) as would give the drug molecule a closer structural resemblance to riboflavin (II), in view of the possible parallelism between antimalarial activity and the antagonism exhibited by type (I) for this

factor, with respect to the growth of *Lactobacillus casei* (Madinaveitia, *Biochem. J.*, 1946, **40**, 373).

(I.) 


(II.)

(III.) 


(IV.)

In Part IV (*ibid.*, p. 362) a major modification of (I) was described in which the anilino-group was replaced by the phenylguanidino-residue giving (III). This led to substances of appreciably enhanced activity against experimental malarial infections and the selection of (III; R = Cl, R′ = H, R″ = $[CH_2]_2$·NEt_2) for clinical investigation in man (Curd, Davey, and Rose, *Ann. Trop. Med. Parasit.*, 1945, **39**, 139). The preparation of a limited number of chemical variants was described in Part IV, but the clinical efficacy of this type called for a more complete study of the effect of changes in molecular detail along the lines followed for the earlier type (I). The chief modifications were as follows:

(a) *Variations in the side chains* R′,R″. Dialkylaminoalkyl groups of varying complexity have been introduced into the molecule, including γ-dimethylaminopropyl which led to high activity when incorporated in the anilinopyrimidines (type I) (see Part I), others in which ether, thioether, amino- and phenyl groupings were interposed, and in addition bis(dialkylamino)-alkyl groups. The NR′R″ (III) group has also been derived from secondary amines such as ethyl-β-diethylaminoethylamine and diethylamine. The use of simple amine residues such as the latter was considered justifiable since it was thought that omission of the basic centre in the alkyl side chain would be balanced in part by the increased basicity of type (III), as compared with type (I), owing to the presence in the molecule of the guanidine group. The two general methods described in Part (IV) for the preparation of 2-*p*-chlorophenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine were used throughout for the introduction of the group NR′R″, namely, reaction between the 4-chloropyrimidine and the appropriate amine, either in acetic acid at temperatures up to 130°, or under reflux in a mixture of chlorobenzene and dilute sodium hydroxide. In general, the latter method gave the better yields. A single preparation of a related substance, in which NR′R″ was replaced by the methyl group giving 2-p-*chlorophenylguanidino*-4 : 6-*dimethylpyrimidine* (III; R = Cl, NR′R″ = Me), was made by reaction of *p*-chlorophenyldiguanide with acetylacetone in acetic acid in the presence of anhydrous sodium acetate. It was assumed that, by analogy with the β-keto-ester reaction, condensation occurred between the diketone and the terminal pair of nitrogen atoms of the diguanide.

(b) *Variation of the substituents in the phenyl group.* This aspect of the investigation has followed closely the variations made in type (I) and described in Parts I and II, thus enabling comparisons to be made of the effect on antimalarial activity of similar substitution in both types (I) and (III). An attempt was made to introduce the sulphonamide grouping into the molecule, not on account of its significance in the sulphanilamide type of drug, but because the inductive effect of such a grouping was in the same sense as that of cyano-, nitro-, and halogeno- which had earlier been shown to promote positive antimalarial activity. The requisite synthesis was successful up to the preparation of 4-*hydroxy*-2-p-*sulphonamidophenylguanidino*-6-*methylpyrimidine*, but the isolation of the corresponding 4-chloropyrimidine in a pure form was not achieved and reaction of this crude intermediate with β-diethylaminoethylamine gave intractable products. Synthesis of the related 2-*p*-sulphondimethylamidophenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine was, however, successful at all stages, and failure with the unsubstituted sulphonamido-compound can probably be attributed to the presence in the latter of easily replaceable hydrogen atoms which result in self-condensation at the chloropyrimidine stage. A sulphone group was also introduced into type (III) by the preparation of 2-p-*methylsulphonylphenylguanidino*-4-β-*diethylaminoethylamino*-6-*methylpyrimidine* (III, R = SO_2·Me, R′ = H, R″ = $[CH_2]_2$·NEt_2).

The observation by Madinaveitia (*loc. cit.*) that (III; R = Cl, R′ = H, R″ = $[CH_2]_2$·NEt_2), like type (I), behaved as a riboflavin antagonist with respect to the growth of *L. casei*, suggested that substitution of methyl groups in positions 3 and 4 of the benzene ring (corresponding to the 5 : 6-dimethylbenz-portion of riboflavin) would be of interest, and accordingly

2-(4′-o-*xylyl*)*guanidino*-4-β-*diethylaminoethylamino*-6-*methylpyrimidine* (IV; R = 3 : 4-$C_6H_3Me_2$, R′ = H, R″ = $[CH_2]_2{\cdot}NEt_2$, X = H, Y = Me) was prepared.

The synthesis of substances of type (III), variously substituted in the aromatic ring, followed closely the two methods used in Part IV, namely the preparation of the required hydroxypyrimidines by interaction of ethyl acetoacetate with the aryldiguanide, or of the arylamine hydrochloride with 2-cyanoamino-4-hydroxy-6-methylpyrimidine, followed by conversion with phosphoryl chloride into the chloropyrimidine, which was then caused to react by one or other of the methods indicated above with the side-chain amine.

(c) *Variation of the substituents in the 5 and 6 position of the pyrimidine ring.* Here again the modifications made in type (I) drugs and described in Part VII (*loc. cit.*) have been applied to type (III), and mainly concern the introduction of alkyl substituents into position 5 (IV; Y = Me, X = alkyl), the substitution of hydrogen or phenyl for the 6-methyl group (IV;

TABLE I.

Antimalarial Activities.

The antimalarial activities were estimated by our colleague Dr. D. G. Davey using chicks infected with *P. gallinaceum*. The meaning of the symbols used to express activity is given in Part I.

Ref. no.	Substance.	Dose, mg./kg.	Activity.
4595	2-*p*-Chlorophenylguanidino-4-β-diethylaminoethylamino-5 : 6-dimethylpyrimidine	40	—
4726	2-*p*-Chlorophenylguanidino-4-γ-diethylaminopropylamino-5 : 6-dimethylpyrimidine	120	++
		40	+
4725	2-*p*-Chlorophenylguanidino-4-β-diethylaminoethylamino-6-methyl-5-ethylpyrimidine	240	—
4851	2-*p*-Chlorophenylguanidino-4-γ-diethylaminopropylamino-6-methyl-5-ethylpyrimidine	80	+
4852	2-*p*-Chlorophenylguanidino-4-γ-diethylaminopropylamino-6-methyl-5-*n*-propylpyrimidine	120	+
4724	2-*p*-Chlorophenylguanidino-4-β-diethylaminoethylamino-6-methyl-5-*n*-butylpyrimidine	120	+
		80	—
4855	2-*p*-Chlorophenylguanidino-4-γ-diethylaminopropylamino-6-methyl-5-*n*-butylpyrimidine	120	+
4853	2-*p*-Chlorophenylguanidino-4-β-diethylaminoethylamino-6-methyl-5-*iso*amylpyrimidine	80	—
4854	2-*p*-Chlorophenylguanidino-4-γ-diethylaminopropylamino-6-methyl-5-*iso*amylpyrimidine	80	—
4596	2-*p*-Chlorophenylguanidino-4-β-diethylaminoethylaminopyrimidine	80	+
5119	2-*p*-Chlorophenylguanidino-4-β-diethylaminoethylamino-6-phenylpyrimidine	80	—
4212	2-*p*-Chlorophenylguanidino-4-β-diethylaminoethylamino-5 : 6-*cyclo*pentenopyrimidine	160	+
		80	—
4289	2-*p*-Chlorophenylguanidino-4-β-diethylaminoethylamino-5 : 6-*cyclo*hexenopyrimidine	160	+
		80	—
3924	2-*p*-Diphenylylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine	120	+
		80	—
3965	2-*p*-Dimethylaminophenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine	160	—
3951	2-*p*-Sulphondimethylamidophenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine	200	—
3999	2-(2′ : 5′-Dichlorophenyl)guanidino-4-β-diethylaminoethylamino-6-methylpyrimidine	120	+
4019	2-(5′-Chloro-2′-methoxyphenyl)guanidino-4-β-diethylaminoethylamino-6-methylpyrimidine	200	+
4060	2-*p*-Methylthiophenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine	200	++
		120	+
4328	2-(3′ : 5′-Dichlorophenyl)guanidino-4-β-diethylaminoethylamino-6-methylpyrimidine	160	++
		80	++
3553	2-*p*-Tolylguanidino-γ-diethylaminopropylamino-6-methylpyrimidine	160	+
3796	2-*m*-Tolylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine	160	+
3803	2-*o*-Tolylguanidino-4-γ-diethylaminopropylamino-6-methylpyrimidine	160	+
		80	—
3950	2-*p*-Methylsulphonylphenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine	200	+
		40	—
3974	2-(5′-Chloro-*o*-tolyl)guanidino-4-β-diethylaminoethylamino-6-methylpyrimidine	80	+
		40	—
3746	2-(4′-*o*-Xylyl)guanidino-4-β-diethylaminoethylamino-6-methylpyrimidine	200	+
3600	2-β-Naphthylguanidino-4-γ-diethylaminopropylamino-6-methylpyrimidine	160	+

TABLE I—*continued.*

Ref. no.	Substance.	Dose, mg./kg.	Activity.
3877	2-Phenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine	160	+
4378	2-*p*-Chlorophenylguanidino-4-diethylamino-6-methylpyrimidine	80	±
4386	2-*p*-Chlorophenylguanidino-4-methyl*iso*propylamino-6-methylpyrimidine	120	+
3765	2-*p*-Chlorophenylguanidino-4-piperidino-6-methylpyrimidine	160	+
3741	2-*p*-Chlorophenylguanidino-4-γ-dimethylaminopropylamino-6-methylpyrimidine	160	+
4384	2-*p*-Chlorophenylguanidino-4-β-pyrrolidinoethylamino-6-methylpyrimidine	40	+
4379	2-*p*-Chlorophenylguanidino-4-ethyl-β-diethylaminoethylamino-6-methylpyrimidine	40	+
4327	2-*p*-Chlorophenylguanidino-4-γ-*n*-butylaminopropylamino-6-methylpyrimidine	400 120	+ —
4096	2-*p*-Chlorophenylguanidino-4-methyl-β-diethylaminoethylamino-6-methylpyrimidine	160	+
3672	2-*p*-Chlorophenylguanidino-4-γ-diethylaminoproylamino-6-methylpyrimidine	200 80	+ —
4110	2-*p*-Chlorophenylguanidino-4-γ-*n*-dibutylaminopropylamino-6-methylpyrimidine	80	+
4261	2-*p*-Chlorophenylguanidino-4-β-piperidino-α-methylethylamino-6-methylpyrimidine	80 40	++ +
4250	2-*p*-Chlorophenylguanidino-4-*p*-(β-diethylaminoethylthio)phenylamino-6-methylpyrimidine	160	+
4392	2-*p*-Chlorophenylguanidino-4-γ-(β′-diethylaminoethoxy)propylamino-6-methylpyrimidine	120	+
4403	2-*p*-Chlorophenylguanidino-4-γ-methyl-β′-diethylaminoethylaminopropylamino-6-methylpyrimidine	240 120	+ —
4411	2-*p*-Chlorophenylguanidino-4-ββ′-bis(diethylamino)*iso*propylamino-6-methylpyrimidine	160 80	+ —
4514	2-*p*-Chlorophenylguanidino-4-bis-(β-diethylaminoethyl)amino-6-methylpyrimidine	320 160	+ —
4380	2-*p*-Chlorophenylguanidino-4 : 6-dimethylpyrimidine	160	++

X = H, Y = H or Ph), and the formation of a *cyclo*penteno- or *cyclo*hexeno-ring across positions 5 and 6 (IV; X and Y = $[CH_2]_3$ or $[CH_2]_4$). In the last process, the product is a 5 : 6 : 7 : 8-tetrahydroquinazoline derivative and therefore related to the active 2-*p*-chloroanilino-4-substituted-aminoquinazolines described in Part XIV (*J.*, 1947, 775). Preparation of many of the intermediate 4-hydroxy-2-*p*-chlorophenylguanidinopyrimidines has been through both the diguanide and the 2-cyanoaminopyrimidine routes. In general, the latter method has given the more satisfactory result, both as regards purity of the crude condensation product and yield. A notable difference in yield was observed in the production of the cyanoaminopyrimidine intermediates from ethyl *cyclo*pentanone- and *cyclo*hexanone-2-carboxylate, the latter reacting much more easily and efficiently with dicyandiamide in the presence of sodium methoxide. The reduced yields observed when the aryldiguanides were employed were due to the formation of by-products, probably 1 : 3 : 5-triazines (cf. Part IV), which, however, were not further investigated.

EXPERIMENTAL.

2-p-*Chlorophenylguanidino*-4-β-*diethylaminoethylamino*-5 : 6-*dimethylpyrimidine* (IV; R = *p*-C_6H_4Cl, R′ = H, R″ = $[CH_2]_2$·NEt_2, X = Y = Me) (4595).—(a) 4-H*ydroxy*-2-p-*chlorophenylguanidino*-5 : 6-*dimethylpyrimidine* was precipitated (yield, 57 g.) when a solution from *p*-chlorophenyldiguanide (62 g.), 11N-sodium hydroxide (33 c.c.), and methanol (200 c.c.) was stirred for 70 hours with ethyl α-methylacetoacetate at 20°. A single extraction with hot dilute acetic acid and lixiviation with hot ethanol left a crystalline solid, m. p. 263° (decomp.) (Found: C, 52·6; H, 4·65; N, 23·95; Cl, 11·7. $C_{13}H_{14}ON_5Cl$ requires C, 53·5; H, 4·8; N, 24·0; Cl, 12·2%). The same hydroxypyrimidine (m. p. and mixed m. p.) was also obtained by refluxing for 17 hours *p*-chloroaniline (8·7 g.), β-ethoxyethanol (70 c.c.), 10N-hydrochloric acid (6·7 c.c.), water (17 c.c.), and the 2-cyanoamino-4-hydroxy-5 : 6-dimethylpyrimidine [m. p. 281° (decomp.), 10·9 g.] prepared by refluxing for 2 hours a mixture of ethyl α-methylacetoacetate (14·4 g.), dicyandiamide (8·4 g.), and sodium (2·3 g.) dissolved in ethanol (65 c.c.).

(b) 4-*Chloro*-2-p-*chlorophenylguanidino*-5 : 6-*dimethylpyrimidine* was obtained by stirring for 1½ hours at 78—84° a mixture of the above crude hydroxypyrimidine (52·5 g.), phosphoryl chloride (18 c.c.), and chlorobenzene (77 c.c.), and adding it to crushed ice and water (360 c.c.) and 11N-sodium hydroxide (94 c.c.). After being collected, washed with water and dried in a vacuum (yield, 52·7 g.) it had m. p. 179—181°. Rapid crystallisation of a little from ethanol gave colourless needles, m. p. 188° (Found: C, 50·05; H, 3·9; N, 22·3; Cl, 22·3. $C_{13}H_{13}N_5Cl_2$ requires C, 50·3; H, 4·1; N, 22·6; Cl, 22·9%).

(c) The crude chloropyrimidine (38 g.), β-diethylaminoethylamine (17·7 g.), chlorobenzene (108 c.c.), and 2·5N-sodium hydroxide (166 c.c.) were refluxed for 2 hours. The chlorobenzene was distilled off in

steam. The residual solid, dissolved at 60° in water (1 l.) and acetic acid (25 c.c.), treated with charcoal, and reprecipitated with sodium hydroxide, gave crude 2-p-*chlorophenylguanidine*-4-*β*-*diethylamino*-*ethylamino*-5 : 6-*dimethylpyrimidine* (39·9 g.), m. p. 70—90°. After crystallisation from light petroleum (b. p. 100—120°) it had m. p. 113°, and it was then converted into the colourless crystalline *dihydrochloride*, m. p. 181—183°, by adding N-hydrochloric acid (2 equivs.) to a solution in acetone (Found : C, 45·3; H, 6·8; N, 19·7. $C_{19}H_{28}N_7Cl,2HCl,2H_2O$ requires C, 45·8, H, 7·0; N, 19·7%). Treatment of an aqueous solution with sodium hydroxide gave the base, m. p. 121—122°, after crystallisation twice from ligroin (Found : N, 25·0. $C_{19}H_{28}N_7Cl$ requires N, 25·1%).

2-p-*Chlorophenylguanidino*-4-*γ*-*diethylaminopropylamino*-5 : 6-*dimethylpyrimidine* (IV; R = *p*-C_6H_4Cl, R′ = H, R″ = $[CH_2]_3{\cdot}NEt_2$, X = Y = Me) (4726).—Similarly prepared using *γ*-diethylaminopropylamine, this *base* formed crystals from ligroin, m. p. 112—113° (Found : C, 59·1; H, 7·2; N, 24·2; Cl, 9·1. $C_{20}H_{30}N_7Cl$ requires C, 59·4; H, 7·4; N, 24·2; Cl, 8·8%).

2-p-*Chlorophenylguanidino*-4-*β*-*diethylaminoethylamino*-6-*methyl*-5-*ethylpyrimidine* (IV; R = *p*-C_6H_4Cl, R′ = H, R″ = $[CH_2]_2{\cdot}NEt_2$, X = Et, Y = Me) (4725).—Similarly prepared from 4-chloro-2-*p*-chlorophenylguanidino-6-methyl-5-ethylpyrimidine (m. p. 194—196° from methanol, 19·6 g.), *β*-diethylaminoethylamine (9·8 g.), chlorobenzene (53 c.c.), and 2·5N-sodium hydroxide (82 c.c.), refluxed for 5 hours, this *base* had m. p. 135—137° (yield, 15·3 g.) from ligroin (Found : C, 59·0; H, 7·2; N, 23·5. $C_{20}H_{30}N_7Cl$ requires C, 59·4; H, 7·4; N, 24·2%). The intermediate 4-hydroxy-2-*p*-chlorophenylguanidino-6-methyl-5-ethylpyrimidine, m. p. 259—261°, was formed in only low yield from *p*-chlorophenyldiguanide and ethyl *α*-ethylacetoacetate. Higher overall yields were obtained by interaction of *p*-chloroaniline, as for 4595, with 2-cyanoamino-4-hydroxy-6-methyl-5-ethylpyrimidine [m. p. 261° (decomp.)].

2-p-*Chlorophenylguanidino*-4-*γ*-*diethylaminopropylamino*-6-*methyl*-5-*ethylpyrimidine* (IV; R=*p*-C_6H_4Cl, R′ = H, R″ = $[CH_2]_3{\cdot}NEt_2$, X = Et, Y = Me) (4851).—Similarly prepared using *γ*-diethylaminopropylamine, this *base* had m. p. 116—118° from ligroin (Found C, 61·1; H, 7·9; N, 23·5. $C_{21}H_{32}N_7Cl$ requires C, 60·4; H, 7·7; N, 24·45%).

2-p-*Chlorophenylguanidino*-4-*γ*-*diethylaminopropylamino*-6-*methyl*-5-n-*propylpyrimidine* (IV; R = *p*-C_6H_4Cl, R′ = H, R″ = $[CH_2]_3{\cdot}NEt_2$, X = Pr^n, Y = Me) (4852).—Similarly prepared from 4-*chloro*-2-p-*chlorophenylguanidino*-6-*methyl*-5-n-*propylpyrimidine* (m. p. 201—202° from methanol) (Found : C, 53·6; H, 4·95; N, 20·2; Cl, 20·6. $C_{15}H_{17}N_5Cl_2$ requires C, 53·25; H, 5·05; N, 20·7; Cl, 21·0%) and *γ*-diethylaminopropylamine, this gave a *dihydrochloride* from acetone, m. p. 114—116° (Found : C, 46·15; H, 7·3; N, 16·9; Cl′, 11·8. $C_{22}H_{34}N_7Cl,2HCl,3H_2O$ requires C, 45·8; H, 7·6; N, 16·9; Cl′, 12·3%). The intermediate 4-hydroxy-2-*p*-chlorophenylguanidino-6-methyl-5-*n*-propylpyrimidine had m. p. 242° from methanol and was prepared both by the diguanide route and from 2-cyanoamino-4-hydroxy-6-methyl-5-*n*-propylpyrimidine (m. p. 233—234° from water).

2-p-*Chlorophenylguanidino*-4-*β*-*diethylaminoethylamino*-6-*methyl*-5-n-*butylpyrimidine* (IV; R = *p*-C_6H_4Cl, R′ = H, R″ = $[CH_2]_2{\cdot}NEt_2$, X = Bu^n, Y = Me) (4724).—Similarly prepared and converted into the dihydrochloride and thence into the *base*, which had m. p. 108—109° from ligroin (Found : C, 60·85; H, 7·6; N, 22·5. $C_{22}H_{34}N_7Cl$ requires C, 61·1; H, 7·8; N, 22·7%). The intermediate chloropyrimidine formed colourless needles from methanol, m. p. 194°, and the corresponding hydroxypyrimidine had m. p. 228—229° from ethanol.

2-p-*Chlorophenylguanidino*-4-*γ*-*diethylaminopropylamino*-6-*methyl*-5-n-*butylpyrimidine* (IV; R = *p*-C_6H_4Cl, R′ = H, R″ = $[CH_2]_3{\cdot}NEt_2$, X = Bu^n, Y = Me) (4855).—Similarly prepared, this formed a *dihydrochloride* from acetone, m. p. 113—115° (Found : C, 48·2; H, 7·25; N, 16·15; Cl′, 12·5. $C_{23}H_{36}N_7Cl,2HCl,3H_2O$ requires C, 48·2; H, 7·7; N, 17·1; Cl′, 12·4%).

2-p-*Chlorophenylguanidino*-4-*β*-*diethylaminoethylamino*-6-*methyl*-5-iso*amylpyrimidine* (IV; R = *p*-C_6H_4Cl, R′ = H, R″ = $[CH_2]_2{\cdot}NEt_2$, X = Am$^\beta$, Y = Me) (4853).—Similarly prepared from 4-chloro-2-*p*-chlorophenylguanidino-6-methyl-5-*iso*amylpyrimidine (m. p. 202° from methanol), this *base* formed colourless crystals from ligroin, m. p. 119—120° (Found : C, 62·35; H, 8·05; N, 22·35. $C_{23}H_{36}N_7Cl$ requires C, 61·95; H, 8·1; N, 22·0%). The intermediate hydroxypyrimidine (from *p*-chlorophenyldiguanide and ethyl *iso*amylacetoacetate, or from *p*-chloroaniline hydrochloride and 2-cyanoamino-4-hydroxy-6-methyl-5-*iso*amylpyrimidine, m. p. 248—250° from methanol) had m. p. 238° from methanol.

2-p-*Chlorophenylguanidino*-4-*γ*-*diethylaminopropylamino*-6-*methyl*-5-iso*amylpyrimidine* (IV; R = *p*-C_6H_4Cl, R′ = H, R″ = $[CH_2]_3{\cdot}NEt_2$, X = Am$^\beta$, Y = Me) (4854).—Similarly prepared using *γ*-diethylaminopropylamine and purified as the *dihydrochloride* which had m. p. 139—141° from acetone (Found : C, 48·65; H, 7·55; N, 16·95; Cl′, 12·5. $C_{24}H_{38}N_7Cl,2HCl,3H_2O$ requires C, 49·1; H, 7·8; N, 16·7; Cl′, 12·1%).

2-p-*Chlorophenylguanidino*-4-*β*-*diethylaminoethylaminopyrimidine* (IV; R = *p*-C_6H_4Cl, R′ = H, R″ = $[CH_2]_2{\cdot}NEt_2$, X = Y = H) (4596).—Similarly prepared from 4-chloro-2-*p*-chlorophenylguanidinopyrimidine (m. p. 156—158° from methanol), this *base* formed colourless needles from toluene, m. p. 191·5—192·5° (Found : C, 56·7; H, 6·4; N, 26·25. $C_{17}H_{24}N_7Cl$ requires C, 56·4; H, 6·6; N, 27·1%). The intermediate hydroxypyrimidine (from *p*-chlorophenyldiguanide and ethyl formylacetate, or from *p*-chloroaniline hydrochloride and 2-cyanoamino-4-hydroxypyrimidine, m. p. >310°) had m. p. 257°.

2-p-*Chlorophenylguanidino*-4-*β*-*diethylaminoethylamino*-6-*phenylpyrimidine* (IV; R = *p*-C_6H_4Cl, R′ = H, R″ = $[CH_2]_2{\cdot}NEt_2$, X = H, Y = Ph) (5119).—*p*-Chlorophenyldiguanide (17·8 g.), ethyl benzoylacetate (15 c.c.), and ethanol (40 c.c.) were refluxed for 7 hours. The precipitate after extraction with hot methanol gave colourless prisms (3 g.) from nitrobenzene of 2-p-*chlorophenylguanidino*-4-*hydroxy*-6-*phenylpyrimidine*, m. p. 254° (Found : C, 58·9; H, 4·4; N, 20·25. $C_{17}H_{14}ON_5Cl$ requires C, 60·0; H, 4·1; N, 20·6%). Treatment with phosphoryl chloride gave the corresponding chloropyrimidine. 2-p-*Chlorophenylguanidino*-4-*β*-*diethylaminoethylamino*-6-*phenylpyrimidine* from the latter and *β*-diethylaminoethylamine formed colourless needles from light petroleum (b. p. 100—120°), m. p. 166—167° (Found : N, 22·15. $C_{23}H_{28}N_7Cl$ requires N, 22·4%).

2-p-*Chlorophenylguanidino*-4-*β*-*diethylaminoethylamino*-5 : 6-cyclo*pentenopyrimidine* (IV : R = *p*-$C_6H_4{\cdot}Cl$, R′ = H, R″ = $[CH_2]_2{\cdot}NEt_2$, XY = $[CH_2]_3$) (4212).—(a) 2-*Cyanoamino*-4-*hydroxy*-5 : 6-cyclo*pentenopyrimidine* prepared by refluxing for 9 hours a mixture of ethyl *cyclo*pentanone-2-carboxylate

(15·6 g.), dicyandiamide (8·4 g.), and sodium (2·3 g.) in methanol (40 c.c.), and then acidifying with acetic acid, formed a colourless solid sparingly soluble in solvents, which when reprecipitated from solution in dilute sodium hydroxide (yield 4·5 g.) darkened and sintered at 240°, finally decomposing at 275° (Found : N, 31·0. $C_8H_8ON_4$ requires N, 31·75%).

(b) 4-*Hydroxy*-2-p-*chlorophenylguanidino*-5 : 6-cyclo*pentenopyrimidine* prepared by refluxing the above 2-cyanoaminopyrimidine (10·6 g.), *p*-chloroaniline (15·4 g.), β-ethoxyethanol (50 c.c.), and 4N-hydrochloric acid (15 c.c.), and purified by adding ammonia to a solution of the crude product in methanol and excess of hydrochloric acid (yield, 6·7 g.), gave colourless needles from β-ethoxyethanol, m. p. 257—258° (Found : C, 55·35; H, 5·35. $C_{14}H_{14}ON_5Cl$ requires C, 55·3; H, 4·6%).

(c) The above hydroxypyrimidine (6·5 g.) and phosphoryl chloride (14 c.c.) were heated for ½ hour at 100° and added to crushed ice and excess of ammonia. An extract of the wet precipitate in water (100 c.c.) and acetic acid (10 c.c.) at 60° gave on cooling and being made alkaline the crude chloropyrimidine (1·8 g., m. p. 162—165°) which after drying in a vacuum over sodium hydroxide was heated for 1½ hours at 95—100° with β-diethylaminoethylamine (0·8 g.) and acetic acid (1 c.c.). Addition of water, filtration, and basification with sodium hydroxide gave 2-p-*chlorophenylguanidino*-4-β-*diethylaminoethylamino*-5 : 6-cyclo*pentenopyrimidine* which formed colourless needles (0·9 g.), m. p. 98—102° from light petroleum (b. p. 100—120°) (Found : C, 60·6; H, 7·1; N, 23·4. $C_{20}H_{28}N_7Cl$ requires C, 59·7; H, 7·0; N, 24·4%).

2 - p - *Chlorophenylguanidino* - 4 - β - *diethylaminoethylamino* - 5 : 6 - cyclo*hexenopyrimidine* (IV; R = *p*-C_6H_4Cl, R′ = H, R″ = $[CH_2]_2$·NEt_2, XY = $[CH_2]_4$) (4289).—(a) 2-*Cyanoamino*-4-*hydroxy*-5 : 6-cyclo*hexenopyrimidine* was obtained crude [m. p. 277° (decomp.)] in good yield (49 g.) by heating under reflux ethyl *cyclo*hexanone-2-carboxylate (51 g.), dicyandiamide (25·2 g.), and sodium (6·9 g.) dissolved in methanol (120 c.c.), and cooling and washing the precipitate, after filtration, with warm very dilute acetic acid. It formed colourless needles from much β-ethoxyethanol, m. p. 278° (decomp.). (Found : C, 56·8; H, 5·3; N, 29·5. $C_9H_{10}ON_4$ requires C, 57·8; H, 5·3; N, 29·1%).

(b) The above cyanoamino-compound (19 g.), refluxed for 3 hours with *p*-chloroaniline (12·8 g.), β-ethoxyethanol (100 c.c.), and 4N-hydrochloric acid (24 c.c.), and worked up as for the *cyclo*penteno-homologue, gave crude 4-*hydroxy*-2-p-*chlorophenylguanidino*-5 : 6-cyclo*hexenopyrimidine* (24·3 g., m. p. 255—257°) which formed colourless needles from β-ethoxyethanol, m. p. 260—261° (Found : C, 56·6; H, 4·9. $C_{15}H_{16}ON_5Cl$ requires C, 56·8; H, 5·25%).

(c) 4-*Chloro*-2-p-*chlorophenylguanidino*-5 : 6-cyclo*hexenopyrimidine*, prepared as for the corresponding *cyclo*penteno-derivative, formed prisms from toluene, m. p. 173—175° (Found : N, 20·6. $C_{15}H_{15}N_5Cl_2$ requires N, 20·8%).

(d) The chloropyrimidine (3·4 g.), β-diethylaminoethylamine (1·45 g.), and acetic acid (1·5 c.c.), heated for 1 hour at 100°, gave 2-p-*chlorophenylguanidino*-4-β-*diethylaminoethylamino*-5 : 6-cyclo*hexenopyrimidine* (1·7 g.) which formed colourless needles from light petroleum (b. p. 100—120°), m. p. 159—160° (Found : C, 62·2; H, 7·4; N, 22·8. $C_{21}H_{30}N_7Cl$ requires C, 62·0; H, 7·2; N, 23·5%).

4-*Hydroxy*-2-*substituted*-*arylguanidino*-6-*methylpyrimidines*.—(*a*) The following were made by interaction of the appropriate *base* with 2-cyanoamino-4-hydroxy-6-methylpyrimidine (method as described above for 4-hydroxy-2-*p*-chlorophenylguanidino-5 : 6-dimethylpyrimidine). 4-*Hydroxy*-2-p-*diphenylylguanidino*-6-*methylpyrimidine* from *p*-aminodiphenyl (16·9 g.) and the cyanoaminopyrimidine (15 g.) (yield of crude product, 12 g.); colourless prisms from benzene, m. p. 261° (Found : C, 70·7; H, 5·9; N, 19·15. $C_{18}H_{17}ON_5,\frac{1}{2}C_6H_6$ requires C, 70·4; H, 5·5; N, 19·55%). 4-*Hydroxy*-2-p-*dimethylaminophenylguanidino*-6-*methylpyrimidine* from *p*-aminodimethylaniline (22 g.) and the cyanoaminopyrimidine (25 g.) (yield of crude product, 28·3 g.); colourless prisms from *o*-dichlorobenzene, m. p. 257—258° (Found : C, 58·7; H, 6·3. $C_{14}H_{18}ON_6$ requires C, 57·7; H, 5·95%). 4-*Hydroxy*-2-p-*sulphondimethylaminophenylguanidino*-6-*methylpyrimidine* from sulphanildimethylamide (14 g.) and the cyanoaminopyrimidine (10·5 g.) (yield of crude product, 8·5 g.); crystals from nitrobenzene, m. p. 259—261° (Found : N, 24·15. $C_{14}H_{18}O_3N_6S$ requires N, 24·0%). 4-*Hydroxy*-2-p-*sulphonamidophenylguanidino*-6-*methylpyrimidine* from sulphanilamide (17·2 g.) and the cyanoaminopyrimidine (15 g.) (yield of crude product, 16·5 g.); insoluble in common organic solvents, and purified by precipitation with ammonia from an aqueous solution of the hydrochloride, m. p. 266—269° (Found : C, 44·8; H, 4·5; N, 25·2. $C_{12}H_{14}O_3N_6S$ requires C, 44·7; H, 4·35; N, 26·1%). 4-*Hydroxy*-2-(2′ : 5′-*dichlorophenyl*)-*guanidino*-6-*methylpyrimidine* from 2 : 5-dichloroaniline (16·2 g.) and the cyanoaminopyrimidine (15 g.) (yield of crude product, 8 g.); purified by addition of dilute ammonia to a solution of the hydrochloride in aqueous β-ethoxyethanol, m. p. 263—266° (Found : C, 45·4; H, 3·6; N, 22·0. $C_{12}H_{11}ON_5Cl_2$ requires C, 46·15; H, 3·5; N, 22·3%). 4-*Hydroxy*-2-(5′-*chloro*-2′-*methoxyphenyl*)*guanidino*-6-*methylpyrimidine*, similarly prepared from 5-chloro-2-methoxyaniline and purified, m. p. 249—250° (Found : N, 22·7. $C_{13}H_{14}O_2N_5Cl$ requires N, 22·75%).

(*b*) The following were made by reaction of the appropriate diguanide with ethylacetoacetate (method as described above for 4-hydroxy-2-*p*-chlorophenylguanidino-5 : 6-dimethylpyrimidine) : 4-*Hydroxy*-2-p-*methylthiophenylguanidino*-6-*methylpyrimidine* from *p*-methylthiophenyldiguanide hydrochloride (18 g.), ethyl acetoacetate (18 c.c.), ethanol (75 c.c.) and 11N-sodium hydroxide (9·7 c.c.), kept for 15 hours (yield of crude product, 16·1 g.); recrystallised from *o*-dichlorobenzene, m. p. 250—252° (Found : C, 53·0; H, 5·3; N, 24·2. $C_{13}H_{15}ON_5S$ requires C, 53·9; H, 5·2; N, 23·4%). 4-*Hydroxy*-2-(3′ : 5′-*dichlorophenyl*)*guanidino*-4-*methylpyrimidine* from 3 : 5-dichlorophenyldiguanide hydrochloride (18·5 g.), ethyl acetoacetate (17 c.c.), ethanol (60 c.c.), and 11N-sodium hydroxide (9·1 c.c.), kept for 16 hours (yield of crude product, 18·75 g.); colourless needles from *o*-dichlorobenzene, m. p. 270—272° (Found : C, 46·15; H, 3·35; N, 22·55. $C_{12}H_{11}ON_5Cl_2$ requires C, 46·2; H, 3·5; N, 22·4%). 4-Hydroxy-2-*p*-tolyl (m. p. 262—264°), -*m*-tolyl (m. p. 241—243°), -*o*-tolyl (m. p. 247—248°), -*p*-methylsulphonylphenyl (m. p. 281°), -5′-chloro-*o*-tolyl (m. p. 252—255°), -4′-*o*-xylyl (m. p. 246—248°), and -β-naphthyl (m. p. 230°)-guanidino-6-methylpyrimidines were made similarly but not obtained analytically pure before proceeding to the next stage.

2-*Substituted*-*aryl*-4-β-*diethylaminoethyl*- (*or* γ-*diethylaminopropyl*-)*amino*-6-*methylpyrimidines* (IV; X = H, Y = Me).—Conversion of the above 4-hydroxypyrimidines into the corresponding

TABLE II.

2-Substituted-arylguanidino-4-dialkylaminoalkylamino-6-methylpyrimidines.

No.	2-Aryl group.	4-Dialkyl-aminoalkyl-amino-group.	Solvent.	M. p.	Formula.	Analysis Found, %. C.	H.	N.	Required, %. C.	H.	N.
3924	*p*-$C_6H_4{\cdot}C_6H_5$	NH·$[CH_2]_2$·NEt_2	Aqueous ethanol	161—163°	$C_{24}H_{31}N_7$	68·7	6·75	23·35	69·1	7·4	23·5
3965	*p*-$C_6H_4{\cdot}NMe_2$	NH·$[CH_2]_2$·NEt_2	Light petroleum (b. p. 100—120°)	183·5—184·5	$C_{20}H_{32}N_6$	62·3	8·25	28·75	62·5	8·3	29·2
3951	*p*-$C_6H_4{\cdot}SO_2{\cdot}NMe_2$	NH·$[CH_2]_2$·NEt_2	Light petroleum (b. p. 100—120°)	149—150	$C_{20}H_{32}O_2N_8S$	53·8	7·65	24·8	53·6	7·15	24·8
3999	2 : 5-$C_6H_3Cl_2$	NH·$[CH_2]_2$·NEt_2	Light petroleum (b. p. 100—120°)	133·5—134·5	$C_{18}H_{25}N_7Cl_2$	53·05	6·3	23·7	52·7	6·1	23·9
4019	3-6-C_6H_3Cl(OMe)	NH·$[CH_2]_2$·NEt_2	Light petroleum (b. p. 100—120°)	145—147	$C_{19}H_{28}ON_7Cl$	56·35	7·1	23·7	56·25	6·9	24·15
4060	*p*-$C_6H_4{\cdot}SMe$	NH·$[CH_2]_2$·NEt_2	Toluene	155—157	$C_{19}H_{29}N_7S$	58·6	7·75	24·7	58·9	7·5	25·3
4328	3 : 5-$C_6H_3Cl_2$	NH·$[CH_2]_2$·NEt_2	Light petroleum (b. p. 100—120°)	158—159	$C_{18}H_{25}N_7Cl_2$	53·1	6·2	23·85	52·7	6·1	23·9
3553	*p*-C_6H_4Me	NH·$[CH_2]_2$·NEt_2	Light petroleum (b. p. 100—120°)	137	$C_{20}H_{31}N_7$	—	—	26·2	—	—	26·5
3796	*m*-C_6H_4Me	NH·$[CH_2]_2$·NEt_2	Light petroleum (b. p. 100—120°)	134—135	$C_{19}H_{29}N_7$	64·05	7·85	27·85	64·2	8·15	27·6
3803	*o*-C_6H_4Me	NH·$[CH_2]_2$·NEt_2	Light petroleum (b. p. 100—120°)	133—133·5	$C_{20}H_{31}N_7$	65·0	8·0	26·3	64·9	8·4	26·5
3950	*p*-$C_6H_4{\cdot}SO_2Me$	NH·$[CH_2]_2$·NEt_2	Toluene	152—154	$C_{19}H_{29}O_2N_7S$	54·4	7·6	22·6	54·4	6·9	23·4
3974	4-6-C_6H_3Cl(Me)	NH·$[CH_2]_2$·NEt_2	Light petroleum (b. p. 100—120°)	138—139	$C_{19}H_{28}N_7Cl$	58·05	7·15	24·8	58·45	7·2	25·1
3746	3 : 4-$C_6H_3Me_2$	NH·$[CH_2]_2$·NEt_2	Light petroleum (b. p. 100—120°)	144—145	$C_{20}H_{31}N_7$	64·9	8·0	25·9	64·9	8·4	26·5
3600	*β*-$C_{10}H_7$	NH·$[CH_2]_2$·NEt_2	Water (as hydrochloride)	102—106	$C_{23}H_{31}N_7$,2HCl,2H_2O	53·1	7·2	19·2	53·7	6·8	19·0
3877	C_6H_5	NH·$[CH_2]_2$·NEt_2	Light petroleum (b. p. 100—120°)	122—122·5	$C_{18}H_{27}N_7$,H_2O	63·65	8·0	27·95	63·2	8·0	27·95

TABLE III.

2-p-Chlorophenylguanidino-4-substituted-amino-6-methylpyrimidines.

No.	4-Substituted-amino-group.	Solvent.	M. p.	Formula.	Analysis. Found, %. C.	H.	N.	Required, %. C.	H.	N.
4378	NEt_2	Light petroleum (b. p. 100—120°)	152—153·5°	$C_{16}H_{21}N_6Cl$	57·1	5·9	24·55	57·75	6·3	25·25
4386	$NMePr^{\beta}$	Toluene	186—187·5	$C_{16}H_{21}N_6Cl$	57·3	6·2	24·65	57·75	6·3	25·25
3765	NC_5H_{10}	Butanol (hydrochloride)	253—254	$C_{17}H_{21}N_6Cl$,HCl	53·35	6·0	21·8	53·5	5·8	22·1
3741	NH·$[CH_2]_2$·NMe_2	Toluene	182—184	$C_{17}H_{24}N_7Cl$	55·6	6·4	25·6	56·35	6·6	27·05
4384	NH·$[CH_2]_2$·NC_4H_8	Toluene	184—185	$C_{18}H_{24}N_7Cl$	57·9	6·25	25·9	57·85	6·45	26·25
4379	NEt·$[CH_2]_2$·NEt_2	Light petroleum (b. p. 100—120°)	102—103	$C_{20}H_{30}N_7Cl$	59·5	7·65	(Cl, 9·0)	59·45	7·45	(Cl, 8·8)
4327	NH·$[CH_2]_2$·$NHBu^{\alpha}$	Light petroleum (b. p. 100—120°)	136—138	$C_{19}H_{28}N_7Cl$	59·2	6·85	24·8	58·5	7·2	25·15
4096	NMe·$[CH_2]_2$·NEt_2	Light petroleum (b. p. 100—120°)	108—109	$C_{19}H_{28}N_7Cl$	58·05	6·7	25·3	58·5	7·2	25·15
3672	NH·$[CH_2]_2$·NEt_2	Light petroleum (b. p. 100—120°)	144·5—145	$C_{19}H_{28}N_7Cl$	58·85	7·35	24·9	58·5	7·2	25·15
4110	NH·$[CH_2]_2$·NBu_2^{α}	Acetone	93— 94	$C_{23}H_{36}N_7Cl$	61·95	7·5	21·75	61·95	8·1	21·9
4261	NH·CHMe·CH_2·NC_5H_{10}	Light petroleum (b. p. 100—120°)	143—144	$C_{20}H_{28}N_7Cl$	60·05	6·55	23·9	59·7	6·95	24·4
4250	*p*-NH·$C_6H_4{\cdot}S{\cdot}[CH_2]_2{\cdot}NEt_2$	Light petroleum (b. p. 100—120°	146—147	$C_{24}H_{30}N_7SCl$	59·45	6·1	19·55	59·4	6·2	20·2
4392	NH·$[CH_2]_2$·O·$[CH_2]_2$·NEt_2	Light petroleum (b. p. 100—120°)	123—124	$C_{21}H_{32}ON_7Cl$	57·55	6·9	22·7	58·1	7·4	22·6
4403	NH·$[CH_2]_2$·NMe·$[CH_2]_2$·NEt_2	Toluene	119—120	$C_{22}H_{35}N_8Cl$	59·1	7·75	24·25	59·05	7·85	25·05
4411	NH·CH(CH_2·NEt_2)$_2$	Light petroleum (b. p. 100—120°)	111—113	$C_{23}H_{37}N_8Cl$	60·1	7·6	23·9	59·95	8·05	24·3
4514	N($[CH_2]_2$·NEt_2)$_3$	Water (trihydriodide)	158—162	$C_{24}H_{39}N_8Cl$,3HI	33·3	5·15	12·65	33·65	4·6	13·05

4-chloropyrimidines and interaction of the latter with either β-diethylaminoethylamine or γ-diethylaminopropylamine was by the method described above for 4212. The substances so prepared are contained in Table II. In addition a related substance, 2-p-*aminophenylguanidino*-4-*β-diethylaminoethylamino*-6-*methylpyrimidine* (III, R = NH_2, R′ = H, R″ = $[CH_2]_2 \cdot NEt_2$) (3819) was prepared by reduction of the corresponding nitro-derivative (Curd and Rose, *J.*, 1946, 366) with hydrogen and Raney nickel at ordinary temperature and pressure. It formed colourless needles from light petroleum (b. p. 100—120°), m. p. 143—145° (Found : N, 30·05. $C_{18}H_{28}N_8,H_2O$ requires N, 30·4%).

2-p-*Chlorophenylguanidino*-4-*substituted-amino*-6-*methylpyrimidines* (III; R = Cl).—These compounds, prepared by interaction of 4-chloro-2-*p*-chlorophenylguanidino-6-methylpyrimidine (see Part IV) with the appropriate amines, either in acetic acid or chlorobenzene in the presence of dilute sodium hydroxide, are listed in Table III.

2-p-*Chlorophenylguanidino*-4 : 6-*dimethylpyrimidine* (4380).—*p*-Chlorophenyldiguanide hydrochloride (12·5 g.), acetylacetone (6 g.), anhydrous sodium acetate (8·2 g.), and acetic acid (100 c.c.) were refluxed for 2 hours, added to water (400 c.c.), and made alkaline with sodium hydroxide. The solid was collected, reprecipitated from solution in dilute hydrochloric acid with ammonia, and crystallised from aqueous dioxan. It formed colourless needles, m. p. 204—205° (Found : Cl, 12·3. $C_{13}H_{14}N_5Cl,H_2O$ requires Cl, 12·4%).

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120. *Synthetic Antimalarials. Part XXIV. Some 2-Phenylureido- and 2-Phenylthioureido-4-dialkylaminoalkylamino-6-methylpyrimidines.*

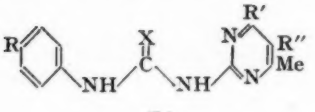
By R. DE B. ASHWORTH, A. F. CROWTHER, F. H. S. CURD, and F. L. ROSE.

The condensation of aryl *iso*cyanates and aryl *iso*thiocyanates with 2-aminopyrimidines has been shown to give 2-arylureido- and 2-arylthioureido-pyrimidines respectively. Compounds of these types carrying dialkylaminoalkylamino-groups in the 4-position which have now been prepared were found to be without significant activity against *P. gallinaceum* in chicks, in contrast to the activity of the corresponding 2-arylguanidino-4-dialkylaminoalkylamino-6-methylpyrimidines.

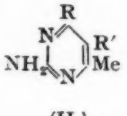
As a result of the discovery of antimalarial activity in 2-*p*-chlorophenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine (Part IV, *J.*, 1946, 362) it was considered to be of interest to determine whether or not such activity was retained in the corresponding compounds in which the guanidine linkage was replaced by urea or thiourea linkages. Previous work indicated three methods by which arylureido- and arylthioureido-pyrimidines might be made. Wheeler and Bristol (*Amer. Chem. J.*, 1905, **33**, 448) first brought a chloropyrimidine into reaction with potassium thiocyanate to give an *iso*thiocyanatopyrimidine, and showed that 2-ethylthio-6-*iso*thiocyanopyrimidine reacted with aniline to give 2-ethylthio-4-phenylthioureidopyrimidine. Reinvestigation of the reaction of 4-chloro-2-ethylthiopyrimidine with potassium thiocyanate by Johnson and Storey (*ibid.*, 1908, **40**, 131) revealed that in this, as in other cases, the first product is the normal thiocyanate which can be isolated under certain conditions and subsequently isomerised to the *iso*thiocyanate. Similar preparations of arylthioureidopyrimidines from *iso*thiocyanatopyrimidines and arylamines have been described by Johnson and McCollum (*ibid.*, 1906, **36**, 136), Johnson and Chi (*J. Amer. Chem. Soc.*, 1930, **52**, 1580), and Chi and his co-workers [*ibid.*, 1932, **54**, 2058; 1933, **55**, 4183, 4655; 1936, **58**, 771, 773; *J. Chem. Eng.* (*China*), 1938, **5**, 35; *Chem. Abs.*, 1939, **33**, 6855], but it would appear that the method is limited in its application since certain chloropyrimidines fail to react with potassium thiocyanate (cf. Johnson and Storey, *loc. cit.*). An analogous method has been used by Chi and Ming (*Trans. Science Soc. China*, 1934, **8**, 77; *Chem. Abs.*, 1935, **29**, 472) for the preparation of a 4-phenylureidopyrimidine, namely ethyl 2-ethylthio-4-phenylureidopyrimidine-5-carboxylate; this involved, at the last stage, condensation of ethyl 2-ethylthio-4-*iso*cyanatopyrimidine-5-carboxylate with aniline. The second method, by which only arylureidopyrimidines have been made, involves the condensation of an aminopyrimidine with an aryl *iso*cyanate (cf. Keller *J. pr. Chem.*, 1885, **31**, 373; Herfeldt, *ibid.*, 1896, **53**, 249; Johnson, Johns, and Heyl, *Amer. Chem. J.*, 1906, **36**, 160). The reaction of an aminopyrimidine with ethyl chloroformate followed by condensation of the product with aniline is recorded by von Meyer (*J. pr. Chem.*, 1884, **30**, 118).

Although there seemed no reason to doubt the constitution of the products obtained by the first method mentioned above, the other two were not held to be unambiguous. Nevertheless we considered that the condensation of an aminopyrimidine with an aryl *iso*cyanate would be the most suitable for the purpose we had in mind, and *p*-chlorophenyl *iso*cyanate was accordingly

condensed with 2-amino-4-β-diethylaminoethylamino-6-methylpyrimidine. The product obtained from a reaction in xylene solution had all the properties expected of the desired 2-p-*chlorophenylureido*-4-β-*diethylaminoethylamino*-6-*methylpyrimidine* (I; X = O, R = Cl, R′ = NH·$[CH_2]_2$·NEt_2, R″ = H), but, as in the condensation product of 4-amino-2 : 6-dimethylpyrimidine (" Kyanmethin ") with phenyl *iso*cyanate (cf. Keller, *loc. cit.*), later formulated as 4-phenylureido-2 : 6-dimethylpyrimidine (Beilstein, **24**, 89), it was conceivable that the *iso*cyanate had reacted with one of the tautomeric forms (II*a*) or II*b*) and that condensation had taken place on one or other of the pyrimidine nitrogen atoms to give one of the alternative structures (III and IV; X = O, R = Cl, R′ = NH·$[CH_2]_2$·NEt_2, R″ = H).



(I.)



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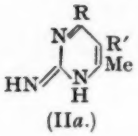
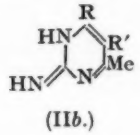
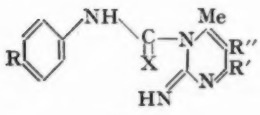


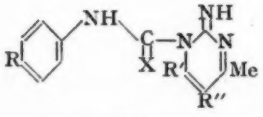
(II*a*.)



(II*b*.)



(III.)



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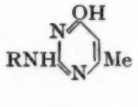

(V.)

These alternative structures were, however, ruled out in the following way. *p*-Chlorophenyl *iso*cyanate was condensed with 2-amino-4-hydroxy-6-methylpyrimidine (II; R = OH, R′ = H) to give 4-*hydroxy*-2-p-*chlorophenylureido*-6-*methylpyrimidine* (I; X = O, R = Cl, R′ = OH, R″ = H), the constitution of which was proved by an alternative synthesis from *p*-chloroaniline and 4-hydroxy-2-ureido-6-methylpyrimidine (V; R = CO·NH_2), the latter being prepared by hydrolysis of 2-cyanoamino-4-hydroxy-6-methylpyrimidine (V; R = CN) (cf. Pohl, *J. pr. Chem.*, 1908, **77**, 542) of which there can no longer be any constitutional doubts in view of the work described in the following paper. When (I; X = O, R = Cl, R′ = OH, R″ = H), made by either method, was treated with phosphoryl chloride it was converted into 4-*chloro*-2-p-*chlorophenylureido*-6-*methylpyrimidine* (I; X = O, R = R′ = Cl, R″ = H), identical with the product of interaction of 4-chloro-2-amino-6-methylpyrimidine (II; R = Cl, R′ = H) with *p*-chlorophenyl *iso*cyanate, and this on interaction with β-diethylaminoethylamine gave 2-*p*-chlorophenylureido-4-β-diethylaminoethylamino-6-methylpyrimidine identical with that originally made from *p*-chlorophenyl *iso*cyanate and (II; R = NH·$[CH_2]_2$·NEt_2, R′ = H). These interconversions not only establish that both 4-chloro-2-*p*-chlorophenylureido-6-methylpyrimidine and 2-*p*-chlorophenylureido-4-β-diethylaminoethylamino-6-methylpyrimidine, like (I; X = O, R = Cl, R′ = OH, R″ = H), have the structures assigned to them and not the possible alternative structures of types (III) and (IV), but also that the condensation of *p*-chlorophenyl *iso*cyanate and 2-amino-4-β-diethylaminoethylamino-6-methylpyrimidine does not involve reaction at the secondary amino-group of the side chain.

The conversion of 2-cyanoamino-4-hydroxy-6-methylpyrimidine into 4-hydroxy-2-*p*-chlorophenylureido-6-methylpyrimidine, although effected in the first instance *via* 4-hydroxy-2-ureido-6-methylpyrimidine, was also carried out through the corresponding *O*-ethyl-*iso*urea. 2-Cyanoamino-4-hydroxy-6-methylpyrimidine, treated with hydrogen chloride in dry alcohol, was converted into [V; R = C(:NH)·OEt] which when heated with *p*-chloroaniline hydrochloride unexpectedly gave (I; X = O, R = Cl, R′ = OH, R″ = H), but with *p*-chloroaniline the anticipated reaction took place and 4-hydroxy-2-*p*-chlorophenylguanidino-6-methylpyrimidine (I; X = NH, R = Cl, R′ = OH, R″ = H) was formed.

4-Chloro-2-*p*-chlorophenylureido-6-methylpyrimidine was also formed by the interaction of 4-chloro-2-amino-6-methylpyrimidine with *p*-chlorophenylurea and with ethyl *p*-chlorophenylurethane, and condensation of (I; X = O, R = R′ = Cl, R″ = H) with γ-diethylaminopropylamine, δ-diethylaminobutylamine, and γ-di-*n*-butylaminopropylamine afforded further examples of 2-*p*-chlorophenylureido-4-dialkylaminoalkylamino-6-methylpyrimidines for test as antimalarials. One compound of the same type, but carrying an alkyl group in the 5-position of the pyrimidine nucleus, namely 2-p-*chlorophenylureido*-4-β-*diethylaminoethylamino*-6-*methyl*-5-*ethylpyrimidine* (I; X = O, R = Cl, R′ = NH·$[CH_2]_2$·NEt_2, R″ = Et) was made by condensing *p*-chlorophenyl *iso*cyanate with 2-amino-4-β-diethylaminoethylamino-6-methyl-5-ethylpyrimidine (II; R = NH·$[CH_2]_2$·NEt_2, R′ = Et).

In addition to the above 2-*p*-chlorophenylureido-4-dialkylaminoalkylamino-6-methylpyrimidines the following were made by condensation of 4-chloro-2-*p*-chlorophenylureido-6-methylpyrimidine with piperidine, morpholine, and di-*n*-butylamine respectively: 2-p-*chlorophenylureido*-4-*piperidino*-, 2-p-*chlorophenylureido*-4-*morpholino*-, and 2-p-*chlorophenylureido*-4-*di*-n-*butylamino*-6-*methylpyrimidine*. These compounds were not considered worth testing as antimalarials in view of the fact that the aforementioned dialkylaminoalkylamino-compounds showed only doubtful activity against *P. gallinaceum* in chicks at maximum tolerated doses.

The behaviour of *p*-chlorophenyl *iso*thiocyanate when brought into reaction with 2-amino-4-dialkylaminoalkylamino-6-methylpyrimidines parallelled that of *p*-chlorophenyl *iso*cyanate. Thus, *p*-chlorophenyl *iso*thiocyanate with (II; R = NH·$[CH_2]_2$·NEt_2, R′ = H) and 2-*amino*-4-*γ*-*diethylaminopropylamino*-6-*methylpyrimidine* (II; R = NH·$[CH_2]_3$·NEt_2, R′ = H) gave 2-p-*chlorophenylthioureido*-4-β-*diethylaminoethylamino*- (I; X = S, R = Cl, R′ = NH·$[CH_2]_2$·NEt_2, R″ = H) and 2-p-*chlorophenylthioureido*-4-*γ*-*diethylaminopropylamino*-6-*methylpyrimidine* (I; X = S, R = Cl, R′ = NH·$[CH_2]_3$·NEt_2, R″ = H). The constitutions of these substances were established by their conversion, with the aid of alcoholic ammonia and mercuric oxide, into the corresponding guanidino-compounds, 2-*p*-chlorophenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine (I; X = NH, R = Cl, R′ = NH·$[CH_2]_2$·NEt_2, R″ = H) (Part IV, *loc. cit.*) and 2-*p*-chlorophenylguanidino-4-*γ*-diethylaminopropylamino-6-methylpyrimidine (I; X = NH, R = Cl, R′ = NH·$[CH_2]_3$·NEt_2, R″ = H) (Part XXIII, preceding paper). (The constitutions of these guanidinopyrimidines are unequivocally proved by the work described in the following paper.)

The above thioureidopyrimidines and other similar compounds synthesised, namely 2-p-*bromophenylthioureido*-4-β-*diethylaminoethylamino*-6-*methylpyrimidine* (I; X = S, R = Br, R′ = NH·$[CH_2]_2$·NEt_2, R″ = H), 2-p-*chlorophenylthioureido*-4-δ-*diethylamino*-α-*methylbutylamino*-6-*methylpyrimidine* (I; X = S, R = Cl, R′ = NH·CHMe·$[CH_2]_3$·NEt_2, R″ = H), and 2-p-*chlorophenylthioureido*-4-β-*diethylaminoethylamino*-6-*methyl*-5-*ethylpyrimidine* (I; X = S, R = Cl, R′ = NH·$[CH_2]_2$·NEt_2, R″ = Et) were found to be inactive against *P. gallinaceum* in chicks when tested by our colleague, Dr. D. G. Davey.

The above work suggested that *p*-chlorophenylcyanamide should condense with 2-aminopyrimidines to give 2-*p*-chlorophenylguanidinopyrimidines, and after numerous abortive attempts it was found that condensation with 2-amino-4-β-diethylaminoethylamino-6-methylpyrimidine dihydrochloride did occur in boiling butanol solution to give 2-*p*-chlorophenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine (3349).

Experimental.

4-*Hydroxy*-2-p-*chlorophenylureido*-6-*methylpyrimidine* (I; X = O, R = Cl, R′ = OH, R″ = H).—(*a*) *p*-Chlorophenyl *iso*cyanate (1·6 g.) (Vittenet, *Bull. Soc. chim.*, 1899, **21**, 954), 2-amino-4-hydroxy-6-methylpyrimidine (1·2 g.) (Gabriel and Colman, *Ber.*, 1899, **32**, 2924), and dry xylene (5 c.c.) were boiled under reflux for ½ hour. After cooling, the insoluble material was filtered off, dried, and extracted twice with boiling water (50 c.c.) to leave a white powder which was crystallised first from dimethylformamide and then from nitrobenzene, giving 4-*hydroxy*-2-p-*chlorophenylureido*-6-*methylpyrimidine* as a colourless micro-crystalline powder, m. p. 294° (Found: C, 51·8; H, 4·1; Cl, 12·7. $C_{12}H_{11}O_2N_4Cl$ requires C, 51·7; H, 3·95; Cl, 12·75%).

(*b*) 4-Hydroxy-2-ureido-6-methylpyrimidine (5·4 g.) (Pohl, *loc. cit.*) and *p*-chloroaniline (3·9 g.) were heated in boiling *o*-dichlorobenzene (30 c.c.) for 1½ hours. Ammonia was evolved. The product was collected hot, washed successively with toluene and light petroleum, and dried. Recrystallisation from formodimethylamide and then from nitrobenzene gave the same product as in (*a*), m. p. and mixed m. p. 294° (Found: N, 20·5. $C_{12}H_{11}O_2N_4Cl$ requires N, 20·1%).

4-*Chloro*-2-p-*chlorophenylureido*-6-*methylpyrimidine* (I; X = O, R = R′ = Cl, R″ = H).—(*a*) A solution of *p*-chlorophenyl *iso*cyanate (32 g.) and 4-chloro-2-amino-6-methylpyrimidine (28 g.) (Gabriel and Colman, *loc. cit.*) in dry xylene (150 c.c.) was boiled under reflux for ½ hour. The product, which separated during the reaction, was filtered off after cooling, dried, and crystallised from toluene, giving 4-*chloro*-2-p-*chlorophenylureido*-6-*methylpyrimidine* as a colourless microcrystalline powder, m. p. 224—225° (Found: C, 48·8; H, 3·6; N, 18·6; Cl, 23·6, 24·0. $C_{12}H_{10}ON_4Cl_2$ requires C, 48·5; H, 3·4; N, 18·85; Cl, 23·9%).

(*b*) 4-Hydroxy-2-*p*-chlorophenylureido-6-methylpyrimidine (4 g.) [made by method (*a*) above] and phosphoryl chloride (8 c.c.) were refluxed for 6 minutes and the brownish-yellow solution, after cooling, poured on to a mixture of ice (120 g.) and sodium hydroxide solution (28 c.c. of 35%). The resulting yellowish granular solid was filtered off, dried, and crystallised twice from xylene–butanol (decolorisation being effected with a little activated alumina) to give the same product as in (*a*), m. p. and mixed m. p. 225° (Found: C, 48·2; H, 3·3; Cl, 23·7%).

4-Hydroxy-2-*p*-chlorophenylureido-6-methylpyrimidine, prepared by method (*b*) above, when treated with phosphoryl chloride in exactly the same manner also gave 4-chloro-2-*p*-chlorophenylureido 6-methylpyrimidine, m. p. and mixed m. p. 225°.

(*c*) *p*-Chlorophenylurea (0·8 g.) (Young and Dunstan, *J.*, 1908, **93**, 1058) and 4-chloro-2-amino-6-methylpyrimidine (0·7 g.) were heated in boiling *o*-dichlorobenzene (10 c.c.) until ammonia ceased to be evolved. The product which separated on cooling was filtered off, dried, and crystallised from butanol. It then had m. p. 223—224° alone or admixed with the product made by method (*a*).

(*d*) Ethyl *p*-chlorophenylurethane (2 g.) (Vittenet, *loc. cit.*) was dissolved in *o*-dichlorobenzene (10 c.c.) and the solution added to 4-chloro-2-amino-6-methylpyrimidine (1·4 g.) dissolved in the same solvent (12·5 c.c.). The resulting mixture was refluxed for 3 hours, part of the solvent being allowed to distil off. The product which separated on cooling was filtered off, dried, and crystallised from butanol; m. p. 224° undepressed on admixture with material made by method (*a*).

2-p-*Chlorophenylureido*-4-*β*-*diethylaminoethylamino*-6-*methylpyrimidine* (I; X = O, R = Cl, R′ = NH·[CH_2]$_2$·NEt_2, R″ = H).—(*a*) *p*-Chlorophenyl *iso*cyanate (3·2 g.) in dry xylene (10 c.c.) was added to 2-amino-4-*β*-diethylaminoethylamino-6-methylpyrimidine (4·4 g.) (Part III, *J.*, 1946, 357) in dry xylene (15 c.c.). On heating to boiling, reaction occurred and the product crystallised out. It was filtered off and crystallised from toluene (yield, 51·2%). Recrystallisation from ethyl acetate gave the *product* as colourless prisms, m. p. 199—200° (Found: C, 57·2; H, 6·6; N, 22·6; Cl, 9·4. $C_{18}H_{25}ON_6Cl$ requires C, 57·3; H, 6·6; N, 22·3; Cl, 9·4%) (3921).

(*b*) 4-Chloro-2-*p*-chlorophenylureido-6-methylpyrimidine (9 g.) was added to *β*-diethylaminoethylamine (10·4 g.) in acetic acid (13 c.c.) and the mixture boiled gently under reflux until complete solution was obtained. The mixture was then poured into water (100 c.c.), insoluble material filtered off, and the filtrate added to excess of sodium hydroxide. The washed and dried product was crystallised from toluene and then from dilute alcohol, giving 2-*p*-chlorophenylureido-4-*β*-diethylaminoethylamino-6-methylpyrimidine, m. p. 199—200° undepressed on admixture with material made by method (*a*).

2-p-*Chlorophenylureido*-4-*γ*-*diethylaminopropylamino*-6-*methylpyrimidine* (I; X = O, R = Cl, R′ = NH·[CH_2]$_3$·NEt_2, R″ = H), prepared by method (*b*) above using *γ*-diethylaminopropylamine in place of *β*-diethylaminoethylamine, crystallised from light petroleum (b. p. 100—120°) in colourless flat prisms, m. p. 188—190° (Found: N, 21·5. $C_{19}H_{27}ON_6Cl$ requires N, 21·5%) (4636).

2-p-*Chlorophenylureido*-4-*δ*-*diethylaminobutylamino*-6-*methylpyrimidine* (I; X = O, R = Cl, R′ = NH·[CH_2]$_4$·NEt_2, R″ = H), prepared similarly from 4-chloro-2-*p*-chlorophenylureido-6-methylpyrimidine and *δ*-diethylaminobutylamine, was obtained as colourless needles from ethyl acetate, m. p. 185—186° (Found: N, 20·8. $C_{20}H_{29}ON_6Cl$ requires N, 20·8%) (4637).

2-p-*Chlorophenylureido*-4-*γ*-*di*-n-*butylaminopropylamino*-6-*methylpyrimidine* (I; X = O, R = Cl, R′ = NH·[CH_2]$_3$·NBu^n_2, R″ = H).—4-Chloro-2-*p*-chlorophenylureido-6-methylpyrimidine (3 g.), *γ*-di-*n*-butylaminopropylamine (2·3 g.), chlorobenzene (10 c.c.), water (10 c.c.), and sodium hydroxide (0·6 g.) were refluxed for 1 hour, and the chlorobenzene then removed by steam distillation. The insoluble residue was filtered off, washed with water, and dried. Crystallised first from light petroleum (b. p. 100—120°) and then from ethyl acetate, it was obtained as colourless needles, m. p. 153—154° (Found: N, 19·1. $C_{23}H_{35}ON_6Cl$ requires N, 19·2%) (4638).

2-p-*Chlorophenylureido*-4-*β*-*diethylaminoethylamino*-6-*methyl*-5-*ethylpyrimidine* (I; X = O, R = Cl, R′ = NH·[CH_2]$_2$·NEt_2, R″ = Et).—*p*-Chlorophenyl *iso*cyanate (3·1 g.), 2-amino-4-*β*-diethylaminoethylamino-6-methyl-5-ethylpyrimidine (2·5 g.) (Part III, *loc. cit.*), and dry xylene (10 c.c.) were refluxed for 10 minutes and, after cooling, the *product* was filtered off and crystallised from toluene. It separated as tiny colourless plates, m. p. 169° (Found: N, 20·8; Cl, 9·4. $C_{20}H_{29}ON_6Cl$ requires N, 20·8; Cl, 8·8%) (4105).

2-p-*Chlorophenylureido*-4-*piperidino*-6-*methylpyrimidine* (I; X = O, R = Cl, R′ = N<[CH_2]$_4$>CH_2, R″ = H).—A mixture of 4-chloro-2-*p*-chlorophenylureido-6-methylpyrimidine (1·5 g.), piperidine (2 g.), chlorobenzene (5 c.c.), water (5 c.c.), and sodium hydroxide (0·3 g.) was refluxed for 1 hour. The mixture was then steam distilled and the residual *product* collected, dried, and crystallised from light petroleum (b. p. >120°). It separated as small colourless needles, m. p. 178—179° (Found: N, 20·2. $C_{17}H_{29}ON_5Cl$ requires N, 20·3%).

2-p-*Chlorophenylureido*-4-*morpholino*-6-*methylpyrimidine* (I; X = O, R = Cl, R′ = N<[CH_2]$_4$>O, R″ = H), prepared similarly using morpholine in place of piperidine, crystallised from butanol–xylene as colourless plates, m. p. 223° (Found: N, 20·3. $C_{16}H_{18}O_2N_6Cl$ requires N, 20·1%).

2-p-*Chlorophenylureido*-4-*di*-n-*butylamino*-6-*methylpyrimidine* (I; X = O, R = Cl, R′ = NBu^n_2, R″ = H).—This was prepared in an exactly analogous manner and separated from ethyl acetate as colourless plates, m. p. 157—158° (Found: N, 17·7. $C_{20}H_{28}ON_5Cl$ requires N, 18·0%).

2-p-*Chlorophenylthioureido*-4-*β*-*diethylaminoethylamino*-6-*methylpyrimidine* (I; X = S, R = Cl, R′ = NH·[CH_2]$_2$·NEt_2, R″ = H).—A solution of *p*-chlorophenyl *iso*thiocyanate (37·2 g.) (*Org. Synth.*, Coll. Vol. I, 1st. Edn., 159) and 2-amino-4-*β*-diethylaminoethylamino-6-methylpyrimidine (44·6 g.) in dry xylene (100 c.c.) was refluxed for 1 hour and then cooled. The product was filtered off, washed first with xylene and then with light petroleum (b. p. 40—60°), and dried. Crystallisation from benzene gave 2-p-*chlorophenylthioureido*-4-*β*-*diethylaminoethylamino*-6-*methylpyrimidine* (yield, 73%) as small colourless plates, m. p. 121—122° (Found: N, 21·4; Cl, 9·5; S, 8·3. $C_{18}H_{25}N_6ClS$ requires N, 21·4; Cl, 9·0; S, 8·15%) (4113).

2-p-*Bromophenylthioureido*-4-*β*-*diethylaminoethylamino*-6-*methylpyrimidine* (I; X = S, R = Br, R′ = NH·[CH_2]$_2$·NEt_2, R″ = H), prepared similarly from *p*-bromophenyl *iso*thiocyanate (5 g.) (Dyson and George, *J.*, 1924, **125**, 1702) and 2-amino-4-*β*-diethylaminoethylamino-6-methylpyrimidine (5 g.) in dry xylene (40 c.c.), crystallised from light petroleum (b. p. 100—120°) as colourless plates, m. p. 132° (yield, 62%) (Found: N, 19·0. $C_{18}H_{25}N_6BrS$ requires N, 19·2%) (3978).

2-p-*Chlorophenylthioureido*-4-*β*-*diethylaminoethylamino*-6-*methyl*-5-*ethylpyrimidine* (I; X = S, R = Cl, R′ = NH·[CH_2]$_2$·NEt_2, R″ = Et), from *p*-chlorophenyl *iso*thiocyanate (7 g.) and 2-amino-4-*β*-diethylaminoethylamino-6-methyl-5-ethylpyrimidine (5 g.) in dry xylene (15 c.c.), crystallised from toluene in colourless plates, m. p. 181° (Found: Cl, 8·6. $C_{20}H_{29}N_6ClS$ requires Cl, 8·6%) (4106).

Conversion of 2-p-*Chlorophenylthioureido*-4-*β*-*diethylaminoethylamino*-6-*methylpyrimidine into* 2-p-*Chlorophenylguanidino*-4-*β*-*diethylaminoethylamino*-6-*methylpyrimidine*.—The thioureido-compound

(1·0 g.) was stirred with mercuric oxide (1·0 g.) and methanolic ammonia (20 c.c. of 18%) at room temperature for 2 hours. The mercuric sulphide which had been formed was filtered off and washed with methanol. The filtrate and washings were combined and evaporated on the steam-bath to leave a glassy residue. This was dissolved in dilute acetic acid, the solution treated with decolorising carbon, filtered, and the filtrate added slowly to excess of dilute sodium hydroxide solution. The resulting solid product was filtered off, washed with water, and dried in a vacuum (yield, 84%). Crystallisation from acetone gave 2-*p*-chlorophenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine, m. p. 155°, either alone or mixed with an authentic specimen (Part IV, *loc. cit.*) (Found: N, 25·8. Calc. for $C_{19}H_{26}N_7Cl$: N, 26·1%). With litharge instead of mercuric oxide the same product was obtained crude, in a yield of 87%. Similarly, copper sulphate pentahydrate gave a yield of 84%.

2-*Amino*-4-γ-*diethylaminopropylamino*-6-*methylpyrimidine* (II; R = NH·[CH$_2$]$_3$·NEt$_2$, R′ = H).—A mixture of 4-chloro-2-amino-6-methylpyrimidine (29·85 g.), γ-diethylaminopropylamine (34·8 g.), chlorobenzene (105 c.c.), sodium hydroxide solution (75 c.c. of 35%), and water (105 c.c.) was refluxed with vigorous stirring for 4 hours. After cooling, sodium hydroxide (60 g.) was added with stirring. The two layers were separated and the aqueous layer extracted twice with chlorobenzene (50 c.c.). The chlorobenzene layer and the extracts were combined, dried (NaOH), and the solvent removed by distillation. The residual oil was purified by vacuum distillation, giving 2-*amino*-4-γ-*diethylaminopropylamino*-6-*methylpyrimidine* as a colourless oil, b. p. 217—218°/11 mm., which gradually solidified (yield, 51·5%). It then crystallised from benzene–light petroleum (b. p. 40—60°) as colourless rods, m. p. 80—82° (Found: C, 60·6; H, 9·0. $C_{12}H_{22}N_5$ requires C, 60·7; H, 9·7%).

2-p-*Chlorophenylthioureido*-4-γ-*diethylaminopropylamino*-6-*methylpyrimidine* (I; X = S, R = Cl, R′ = NH·[CH$_2$]$_3$·NEt$_2$, R″ = H).—The preceding compound (11·85 g.) and *p*-chlorophenyl *iso*thiocyanate (9·35 g., 1·1 mols.) were boiled in xylene (20 c.c.) for 45 minutes. The mixture was then cooled, diluted with light petroleum (b. p. 100—120°) (20 c.c.), and the product filtered off, washed with benzene, and dried (yield, 90%). Crystallisation from light petroleum (b. p. 100—120°) containing a little toluene gave the *thioureido*-compound as clusters of pale fawn needles, m. p. 140° (Found: C, 56·4; H, 6·5; N, 20·5; Cl, 8·7; S, 8·1. $C_{19}H_{27}N_6ClS$ requires C, 56·2; H, 6·6; N, 20·6; Cl, 8·7; S, 7·9%) (5219).

Conversion of 2-p-*Chlorophenylthioureido*-4-γ-*diethylaminopropylamino*-6-*methylpyrimidine into* 2-p-*Chlorophenylguanidino*-4-γ-*diethylaminopropylamino*-6-*methylpyrimidine*.—The above compound (1·0 g.), mercuric oxide (1·0 g.), and methanolic ammonia (20 c.c. of 18%) were stirred at 30—40° for 4 hours. After cooling, the mixture was acidified with 2N-hydrochloric acid and excess of sodium sulphide added. With stirring, the filtered solution was run dropwise into excess of sodium hydroxide at 0—5°. The resulting precipitate was filtered off, washed with water, and dried. Crystallisation from acetone afforded 2-*p*-chlorophenylguanidino-4-γ-diethylaminopropylamino-6-methylpyrimidine, m. p. 147°, undepressed on admixture with an authentic sample (see previous paper) (Found: C, 58·2; H, 6·8. Calc. for $C_{19}H_{28}N_7Cl$: C, 58·5; H, 7·2%).

2-p-*Chlorophenylthioureido*-4-δ-*diethylamino*-α-*methylbutylamino*-6-*methylpyrimidine* (I; X = S, R = Cl, R′ = NH·CHMe·[CH$_2$]$_3$·NEt$_2$, R″ = H).—2-Amino-4-δ-diethylamino-α-methylbutylamino-6-methylpyrimidine (8·2 g.) (Hull *et al.*, Part III, *loc. cit.*), *p*-chlorophenyl *iso*thiocyanate (5·8 g., 1·1 mols.), and xylene (13 c.c.) were boiled for 45 minutes and then cooled. The mixture was diluted with benzene and extracted with dilute acetic acid. The acid extract was decolorised with carbon and then run dropwise into excess of ice-cold 2N-sodium hydroxide. The precipitated base was collected, washed with water, and dried. It was converted into its *dihydrochloride*, m. p. 184°, by dissolving it in a slight excess of alcoholic hydrogen chloride and adding ethyl acetate, followed by crystallisation from alcohol–ethyl acetate (yield, 12·0 g.) (Found: C, 48·0; H, 6·6; N, 15·6; Cl, 20·8; S, 6·5. $C_{21}H_{31}N_6ClS,2HCl,H_2O$ requires C, 47·8; H, 6·6; N, 15·9; Cl, 20·2; S, 6·1%) (5241).

2-p-*Chlorophenylguanidino*-4-δ-*diethylamino*-α-*methylbutylamino*-6-*methylpyrimidine* (I; X = NH, R = Cl, R′ = NH·CHMe·[CH$_2$]$_3$·NEt$_2$, R″ = H).—2-*p*-Chlorophenylthioureido-4-δ-diethylamino-α-methylbutylamino-6-methylpyrimidine dihydrochloride (5 g.) was stirred with mercuric oxide (5 g.) and alcoholic ammonia (50 c.c. of 13%) at 35—40° for 4 hours. The mixture was acidified with dilute hydrochloric acid and excess of sodium sulphide added. The mercuric sulphide was filtered off and the filtrate run into ice-cold 2N-sodium hydroxide. The resulting precipitate was collected, washed with water, and dried (yield, 3·6 g.). The base was soluble in cold light petroleum (b. p. 40—60°) and could not be purified by crystallisation from a solvent. It was partly purified by dissolution in dilute acid and reprecipitation with sodium hydroxide (Found: C, 59·2; H, 7·3; N, 22·5; Cl, 8·3; ash, 0·6. $C_{21}H_{32}N_7Cl$ requires C, 60·3; H, 7·6; N, 23·5; Cl, 8·5%). It gave a *dipicrate* which crystallised from 2-ethoxyethanol as a yellow microcrystalline powder, m. p. 204—205° (Found: C, 45·6; H, 4·2; N, 20·8. $C_{21}H_{32}N_7Cl,2C_6H_3O_7N_3$ requires C, 45·2; H, 4·3; N, 20·8%).

Condensation of p-*Chlorophenylcyanamide and* 2-*Amino*-4-β-*diethylaminoethylamino*-6-*methylpyrimidine*.—2-Amino-4-β-diethylaminoethylamino-6-methylpyrimidine (9·92 g.) and alcoholic hydrogen chloride (26·4 c.c. of 12·4% w/v) were mixed and evaporated to dryness. To the residual dihydrochloride, butanol (25 c.c.) was added (the hydrochloride solidified) followed by *p*-chlorophenylcyanamide (6·8 g.) (to be described in a forthcoming communication) and the mixture refluxed for 8 hours. The cooled clear mixture was diluted with benzene and extracted with 0·5N-hydrochloric acid. The acid extract was shaken with a little benzene, separated, decolorised with carbon, and filtered. It was then made strongly alkaline by the addition of 10N-sodium hydroxide and the liberated oil extracted with benzene. Unchanged aminopyrimidine was removed by repeated extraction with water (6 × 500 c.c.), and the benzene solution dried (K_2CO_3) and evaporated. The residual solid was finally crystallised from benzene–light petroleum (b. p. 40—60°) and then from acetone to give 2-*p*-chlorophenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine, m. p. and mixed m. p. 155°.

(Experiments by Dr. E. C. Owen.) N-(4-*Hydroxy*-6-*methyl*-2-*pyrimidyl*)-O-*ethylisourea* [V; R = C(:NH)·OEt].—2-Cyanoamino-4-hydroxy-6-methylpyrimidine (10 g.) was suspended in dry alcohol (50 c.c.), and dry hydrogen chloride passed into the mixture with rapid stirring, the temperature being kept below 10°. When saturated, the mixture was left at room temperature for 2 days. The

solid was then filtered off, washed with alcohol, and dissolved in water (100 c.c.). After filtration from insoluble material the solution was neutralised with sodium hydroxide. On standing, the *product* crystallised. It was filtered off, dried, and crystallised from alcohol, m. p. 212—213° (Found: C, 49·0; H, 6·1; N, 28·6. $C_8H_{12}O_2N_4$ requires C, 49·0; H, 6·1; N, 28·6%).

Condensation of N-(4-*Hydroxy*-6-*methyl*-2-*pyrimidyl*)-O-*ethylisourea with* p-*Chloroaniline Hydrochloride*.—The above *O*-ethylisourea (2 g.) and *p*-chloroaniline hydrochloride (1·65 g.) were fused at 170° for 20 minutes. The fluid melt gradually crystallised during the reaction. After cooling, it was boiled twice with alcohol, and the insoluble material collected, dried, and crystallised from nitrobenzene, giving 4-hydroxy-2-*p*-chlorophenylureido-6-methylpyrimidine, m. p. and mixed m. p. 293—295° (Found: N, 20·1; Cl, 12·8. Calc. for $C_{12}H_{11}O_2N_4Cl$: N, 20·1; Cl, 12·75%).

Condensation of N-(4-*Hydroxy*-6-*methyl*-2-*pyrimidyl*)-O-*ethylisourea with* p-*Chloroaniline*.—The *O*-ethylisourea (2 g.) and *p*-chloroaniline (1·33 g.) were heated for 1·5 hours at 170°. The cooled mixture was repeatedly extracted with boiling alcohol, and the insoluble residue crystallised from nitrobenzene. The product was identified as 4-hydroxy-2-*p*-chlorophenylguanidino-6-methylpyrimidine, m. p. and mixed m. p. 286—287°, depressed on admixture with 4-hydroxy-2-*p*-chlorophenylureido-6-methylpyrimidine.

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121. *Synthetic Antimalarials. Part XXV. Some 4-Arylguanidino-2- and -6-dialkylaminoalkylaminopyrimidines.*

By A. F. CROWTHER, F. H. S. CURD, and F. L. ROSE.

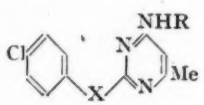
The presumed constitution (Part IV, *J.*, 1946, 362) of the main product of condensation of an aryldiguanide with ethyl acetoacetate has been unequivocally proved to be that of a 2-arylguanidino-4-hydroxy-6-methylpyrimidine by the synthesis, in two cases, of the same compounds from the appropriate arylguanidine and 4-hydroxy-2-methylthio-6-methylpyrimidine.

The study of 2-arylguanidino-4-aminoalkylamino-6-methylpyrimidines, for which these 2-arylguanidino-4-hydroxy-6-methylpyrimidines served as intermediates (Part IV, *loc. cit.*; Part XXIII, this vol., p. 574), has been extended, in the present paper, to include the isomeric 4-arylguanidino-2-dialkylaminoalkylamino-6-methyl- and 4-arylguanidino-6-dialkylaminoalkylamino-2-methyl-pyrimidines. The preferred method of synthesis of these new types involves condensation of an aryl *iso*thiocyanate with 4-amino-2-dialkylaminoalkylamino-6-methylpyrimidines and 4-amino-6-dialkylaminoalkylamino-2-methylpyrimidines respectively, followed by conversion of the resulting arylthioureido-dialkylaminoalkylamino-methylpyrimidines into the corresponding guanidino-compounds by the action of ammonia and a desulphurising agent.

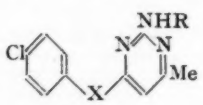
This type of synthesis has also enabled the preparation of 2-arylguanidino-4-dialkylaminoalkylamino-6-methylpyrimidines in which the guanidino-linkage carries an additional alkyl group.

Antimalarial activity is exhibited by all the new types now described.

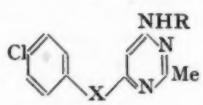
IN this paper we propose to give an account of further arylguanidino-aminoalkylaminopyrimidines which we have investigated following the demonstration of antimalarial activity in compounds of type [I; X = NH·C(:NH)·NH, R = dialkylaminoalkyl] (Part IV, *J.*, 1946, 362) not only against avian malaria but also against human malaria (Adams and Sanderson, *Ann. Trop. Med. Parasit.*, 1945, **39**, 165, 169, 173, 180). Because of the activity of types (I and II; X = NH, R = dialkylaminoalkyl) (*J.*, 1946, 343, 370) which are isomeric, our first objective was the preparation of substances of type [II; X = NH·C(:NH)·NH,



(I.)



(II.)



(III.)

R = dialkylaminoalkyl] similarly related to type [I; X = NH·C(:NH)·NH]: later, substances of type [III; X = NH·C(:NH)·NH, R = dialkylaminoalkyl] were also prepared. The anilino-compounds (III; X = NH) described in Parts VIII (*J.*, 1946, 713) and XXI (*J.*, 1947, 1354) are without activity, and this has been tentatively related to the interdependence of the two amidine systems which does not allow a conjugated path to be traced between the aryl and dialkylaminoalkyl groups *via* alternate carbon and nitrogen atoms in any of the polarised or tautomeric forms of the molecule. Similar considerations apply to [III;

X = NH·C(:NH)·NH] although the incorporation of an additional amidine unit in the bridge between the aryl and pyrimidine nuclei provides in a different manner the system

$$-N{=}C{\cdot}NH{\cdot}C(=NH){\cdot}NH-$$

thought to be essential for antimalarial activity and on which the highly active diguanides described in Part X (*J.*, 1946, 729) were based.

The method of preparation utilised for compounds of type [I; X = NH·C(:NH)·NH] (Part IV, *loc. cit.*) could not be used for the isomeric types [II and III; X = NH·C(:NH)·NH], and different methods of synthesis had to be sought.

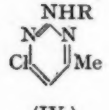
In Part VI (*J.*, 1946, 370) the preparation of compounds of type (II; X = NH) by condensation of a 4-chloro-2-dialkylaminoalkylamino-6-methylpyrimidine (IV) with an arylamine was described, and in Part XV (*J.*, 1947, 783) a similar method was applied to compounds of type (I; X = NH). The condensation of 2-chloro-4-β-diethylaminoethylamino-6-methylpyrimidine (V; R = $[CH_2]_2{\cdot}NEt_2$) and *p*-chlorophenylguanidine (conveniently prepared by interaction of benzoylcyanamide and *p*-chloroaniline hydrochloride followed by hydrolysis of the resulting benzoyl-*p*-chlorophenylguanidine) was therefore tried. Heated together at 110—120° for 18 hours, these compounds reacted to give 2-*p*-chloroanilino-4-β-diethylaminoethylamino-6-methylpyrimidine (I; X = NH, R = $[CH_2]_2{\cdot}NEt_2$) and not the expected 2-*p*-chlorophenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine {I; X = NH·C(:NH)·NH, R = $[CH_2]_2{\cdot}NEt_2$}. The reaction between 4-chloro-2-β-diethylaminoethylamino-6-methylpyrimidine (IV; R = $[CH_2]_2{\cdot}NEt_2$) and *p*-chlorophenylguanidine, which was examined more extensively, proceeded similarly and gave 4-*p*-chloroanilino-2-β-diethylaminoethylamino-6-methylpyrimidine (II; X = NH, R = $[CH_2]_2{\cdot}NEt_2$). One possible explanation of these unexpected results is that the chloropyrimidines condensed with *p*-chlorophenylguanidine on the nitrogen atom carrying the aryl group to give, in the latter case, the compound (VI; R = NH·$[CH_2]_2{\cdot}NEt_2$) which was then degraded to give (II; X = NH, R = $[CH_2]_2{\cdot}NEt_2$). However, the possibility cannot be excluded that, under the reaction conditions, the *p*-chlorophenylguanidine decomposed to give *p*-chloroaniline before condensation. N-p-*Chlorophenyl*-S-*methyl*isothiourea also reacted with (IV; R = $[CH_2]_2{\cdot}NEt_2$) to give 4-*p*-chloroanilino-2-β-diethylaminoethylamino-6-methylpyrimidine as the sole product.

Another synthetic approach to compounds of type [II; X = NH·C(:NH)·NH, R = dialkylaminoalkyl] involving the use of *p*-chlorophenylguanidine was then made in the following way. 2-Hydroxy-4-methylthio-6-methylpyrimidine (Wheeler and McFarland, *Amer. Chem. J.*, 1909, **42**, 431) reacted with *p*-chlorophenylguanidine in boiling *o*-dichlorobenzene to give a product from which 4-*p*-chlorophenylguanidino-2-hydroxy-6-methylpyrimidine [VII; X = NH·C(:NH)·NH, R = OH] was isolated as its *hydrochloride* by extraction with hot dilute hydrochloric acid. For continuation of the synthesis the total acid extract was made alkaline with ammonia and the precipitated product dried and treated with phosphoryl chloride. The resulting chloropyrimidine [VII; X = NH·C(:NH)·NH, R = Cl], without being characterised, was condensed with β-diethylaminoethylamine, γ diethylaminopropylamine, and γ-di-*n*-butylaminopropylamine, by heating either in excess of the aliphatic amine, or in chlorobenzene in presence of aqueous sodium hydroxide, to give poor yields of compounds of type [II; X = NH·C(:NH)·NH] where R = $[CH_2]_2{\cdot}NEt_2$, $[CH_2]_3{\cdot}NEt_2$, and $[CH_2]_3{\cdot}NBu^n_2$ respectively. In each case a by-product was isolated which was insoluble in dilute acetic acid and on retreatment with phosphoryl chloride followed by condensation of the product with γ-dimethylaminopropylamine gave 4-*p*-chloroanilino-2-γ-dimethylaminopropylamino-6-methylpyrimidine (II; X = NH, R = $[CH_2]_3{\cdot}NMe_2$) (cf. Part VI, *loc. cit.*). Again two possible explanations presented themselves. Either the reaction of *p*-chlorophenylguanidine with 2-hydroxy-4-methylthio-6-methylpyrimidine followed two courses, and in addition to the formation of [VII; X = NH·C(:NH)·NH, R = OH] some reaction took place on the nitrogen atom of *p*-chlorophenylguanidine already substituted, to give (VI; R = OH) which then decomposed to give (VII; X = NH, R = OH) and acted as the source of 4-*p*-chloroanilino-2-γ-dimethylaminopropylamino-6-methylpyrimidine in the subsequent transformations; or the *p*-chlorophenylguanidine suffered degradation to *p*-chloroaniline under the conditions of the initial reaction, and the *p*-chloroaniline then reacted with 2-hydroxy-4-methylthio-6-methylpyrimidine to give (VII; X = NH, R = OH). The second explanation seems more likely since it was subsequently demonstrated that *p*-chlorophenylguanidine actually affords some *p*-chloroaniline when heated in boiling *o*-dichlorobenzene for several hours.

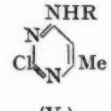
Analogous results were obtained in the condensation of *p*-chlorophenylguanidine and

4-hydroxy-2-methylthio-6-methylpyrimidine. When fused together at 160—170° a product was obtained from which it was possible to isolate 4-hydroxy-2-*p*-chlorophenylguanidino-6-methylpyrimidine [VIII; X = NH·C(:NH)·NH, R = Cl, R′ = OH], but when the crude product from a condensation in boiling *o*-dichlorobenzene was treated with phosphoryl chloride a mixture of chloro-compounds resulted, from which 4-chloro-2-*p*-chloroanilino-6-methylpyrimidine (VIII; X = NH, R = R′ = Cl) was separated in addition to 4-chloro-2-*p*-chlorophenylguanidino-6-methylpyrimidine [VIII; X = NH·C(:NH)·NH, R = R′ = Cl]. Similarly, *p*-anisylguanidine and 4-hydroxy-2-methylthio-6-methylpyrimidine gave 4-hydroxy-2-*p*-anisylguanidino-6-methylpyrimidine [VIII; X = NH·C(:NH)·NH, R = OMe, R′ = OH], identical with that prepared from *p*-anisyldiguanide and ethyl acetoacetate (Part IV, *loc. cit.*).

The identity of the 4-hydroxy-2-*p*-chlorophenylguanidino-6-methylpyrimidine, arising from condensation of *p*-chlorophenylguanidine with 4-hydroxy-2-methylthio-6-methylpyrimidine, with the main product obtained from the reaction of *p*-chlorophenyldiguanide and ethyl acetoacetate (see Part IV) conclusively proves the constitution of the latter, and hence of the compounds of type [I; X = NH·C(:NH)·NH, R = dialkylaminoalkyl] described in Part IV. The only alternative structure which the former might have is (IX), but such a structure could not possibly result from the condensation of *p*-chlorophenyldiguanide and ethyl acetoacetate. The constitution of the product of interaction of dicyandiamide and ethyl acetoacetate as 2-cyanoamino-4-hydroxy-6-methylpyrimidine (Pohl, *J. pr. Chem.*, 1908, **77**, 542) is also thereby rigidly established, since this compound (X; R = CN) not only condenses with arylamines to give 4-hydroxy-2-arylguanidino-6-methylpyrimidines (see Part IV), but reacts with ammonia to give 4-hydroxy-2-guanidino-6-methylpyrimidine [X; R = C(:NH)·NH$_2$] which also condenses with *p*-chloroaniline hydrochloride to give [VIII; X = NH·C(:NH)·NH, R = Cl, R′ = OH].



(IV.)



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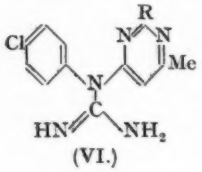
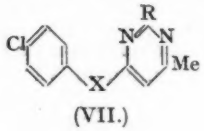
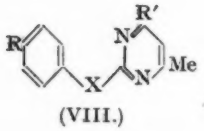


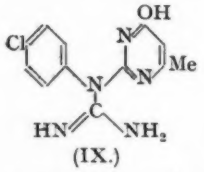
(VI.)



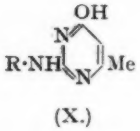
(VII.)



(VIII.)



(IX.)



(X.)

A more convenient method of synthesis of compounds of type [II; X = NH·C(:NH)·NH, R = dialkylaminoalkyl] than that outlined above was provided by a series of reactions analogous to that described in the previous paper for the preparation of 2-*p*-chlorophenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine. 4-Amino-2-β-diethylaminoethylamino-6-methylpyrimidine, prepared by the method of Hull, Lovell, Openshaw, and Todd (Part XI, *J.*, 1947, 41) or by the interaction of 2-chloro-4-amino-6-methylpyrimidine (V; R = H) with β-diethylaminoethylamine, reacted with *p*-chlorophenyl *iso*thiocyanate to give 4-p-*chlorophenylthioureido*-2-β-*diethylaminoethylamino*-6-*methylpyrimidine* (II; X = NH·CS·NH, R = [CH$_2$]$_2$·NEt$_2$) which was then converted by the action of alcoholic ammonia in the presence of copper sulphate into {II; X = NH·C(:NH)·NH, R = [CH$_2$]$_2$·NEt$_2$} identical with the product made by the original route. An attempt to prepare {II; X = NH·C(:NH)·NH, R = CHMe·[CH$_2$]$_3$·NEt$_2$} by the same method was abandoned, since the intermediate product from condensing 4-*amino*-2-δ-*diethylamino*-α-*methylbutylamino*-6-*methylpyrimidine* with *p*-chlorophenyl *iso*thiocyanate could not be obtained crystalline.

Two compounds of the isomeric series were prepared: 4-p-*chlorophenylguanidino*-6-β-*diethylaminoethylamino*-2-*methylpyrimidine* {III; X = NH·C(:NH)·NH, R = [CH$_2$]$_2$·NEt$_2$} and 4-p-*chlorophenylguanidino*-6-γ-*diethylaminopropylamino*-2-*methylpyrimidine* {III; X = NH·C(:NH)·NH, R = [CH$_2$]$_3$·NEt$_2$}, both from the corresponding *thioureas* (III; X = NH·CS·NH, R = [CH$_2$]$_2$·NEt$_2$) and (III; X = NH·CS·NH, R = [CH$_2$]$_3$·NEt$_2$), by interaction with methanolic ammonia in presence of mercuric oxide. The thioureas resulted from the condensation of *p*-chlorophenyl *iso*thiocyanate with 4-amino-6-β-diethylaminoethylamino- and 4-amino-6-γ-diethylaminopropylamino-2-methylpyrimidine, respectively.

The preparation of 2-*p*-chlorophenylguanidino-4-β-diethylaminoethylamino-6-methylpyrimidine from the corresponding thioureido-compound (I; X = NH·CS·NH, R = $[CH_2]_2$·NEt_2) (preceding paper), and the work on the isomeric types now described, suggested a convenient and unambiguous method of synthesis for compounds of type [I; X = NH·C(:NAlkyl)·NH]. For this purpose, 2-*p*-chlorophenylthioureido-4-β-diethylaminoethylamino-6-methylpyrimidine was brought into reaction with methylamine in presence of mercuric oxide to give 2-N¹-p-*chlorophenyl*-N²-*methylguanidino*-N³-4-β-*diethylaminoethylamino*-6-*methylpyrimidine* {I; X = NH·C(:NMe)·NH, R = $[CH_2]_2$·NEt_2}. In a similar manner ethylamine gave 2-N¹-p-*chlorophenyl*-N²-*ethylguanidino*-N³-4-β-*diethylaminoethylamino*-6-*methylpyrimidine* {I; X = NH·C(:NEt)·NH, R = $[CH_2]_2$·NEt_2} and *n*-butylamine gave 2-N¹-p-*chlorophenyl*-N²-n-*butylguanidino*-N³-4-β-*diethylaminoethylamino*-6-*methylpyrimidine* (*dihydrochloride*) {I; X = NH·C(:NBu^n)·NH, R = $[CH_2]_2$·NEt_2}. The same method was also applied to the preparation of 2-*N*¹-*p*-chlorophenyl-*N*²-methylguanidino-*N*³-4-γ-diethylaminopropylamino-6-methylpyrimidine (*trihydrochloride*) {I; X = NH·C(:NMe)·NH, R = $[CH_2]_3$·NEt_2}.

Antimalarial Activities.

The antimalarial activities were estimated against *P. gallinaceum* in chicks by Dr. D. G. Davey, using a method previously described (*Ann. Trop. Med. Parasit.*, 1945, **39**, 139; 1946, **40**, 52). In the summarised results given below activities are expressed in the same way as in Part I (*J.*, 1946, 343).

Ref. no.	Compound.	Dose mg./kg.	Activity.
4924	4-*p*-Chlorophenylguanidino-2-β-diethylaminoethylamino-6-methylpyrimidine	40	+ to ++
4985	4-*p*-Chlorophenylguanidino-2-γ-diethylaminopropylamino-6-methylpyrimidine	80	+
		20	—
4986	4-*p*-Chlorophenylguanidino-2-γ-di-*n*-butylaminopropylamino-6-methylpyrimidine	80	+ to ++
		40	+
		20	±
5227	4-*p*-Chlorophenylthioureido-6-β-diethylaminoethylamino-2-methylpyrimidine	160	Toxic
		80	—
5236	4-*p*-Chlorophenylguanidino-6-β-diethylaminoethylamino-2-methylpyrimidine	80	+
		40	+
5218	4-*p*-Chlorophenylthioureido-6-γ-diethylaminopropylamino-2-methylpyrimidine	80	—
		40	—
5242	4-*p*-Chlorophenylguanidino-6-γ-diethylaminopropylamino-2-methylpyrimidine	120	++
		40	++
		20	+
5165	2-*N*¹-*p*-Chlorophenyl-*N*²-methylguanidino-*N*³-4-β-diethylaminoethylamino-6-methylpyrimidine	40	++
		20	+
5324	2-*N*¹-*p*-Chlorophenyl-*N*²-ethylguanidino-*N*³-4-β-diethylaminoethylamino-6-methylpyrimidine	40	++
		20	++
		10	—
5369	2-*N*¹-*p*-Chlorophenyl-*N*²-*n*-butylguanidino-*N*³-4-β-diethylaminoethylamino-6-methylpyrimidine	80	+
		40	+
5334	2-*N*¹-*p*-Chlorophenyl-*N*²-methylguanidino-*N*³-4-γ-diethylaminopropylamino-6-methylpyrimidine	40	+
		20	+

The following compounds were also tested for prophylactic activity against *P. gallinaceum* but were found to be inactive: **5236**, **5242**, and **5165** at 80 mg./kg.; **5334** at 160 mg./kg.

Experimental.

Benzoylcyanamide.—Diels and Wagner (*Ber.*, 1912, **45**, 876) found that this compound was conveniently made from commercial sodium cyanamide and benzoyl chloride. The following describes its preparation from commercial calcium cyanamide. Finely powdered commercial calcium cyanamide (800 g.) was stirred with water (4 l.) and cooled to 10—15°. Benzoyl chloride (200 c.c.) was added dropwise with stirring at this temperature during 5 hours, and stirring then continued for 16 hours. The mixture was filtered and the residue stirred with water (1½ l.), filtered off, and washed with water (500 c.c.). Calcium chloride (800 g.) was added gradually with cooling to the combined filtrates and washings. The calcium salt of benzoylcyanamide thereby precipitated was collected, drained thoroughly, and dissolved in water (2 l.), and the solution filtered from a little insoluble matter. Hydrochloric acid was added to the filtrate to render it just acid to Congo-red, and the precipitated benzoyl cyanamide collected, washed with water, and dried (yield, 66% on the benzoyl chloride used). Crystallised once from acetone it had m. p. 142—143°. Diels and Wagner (*loc. cit.*) give m. p. 141—142°; Hantzsch and Dollfus (*Ber.*, 1902, **35**, 255) give m. p. 143°.

p-*Chlorophenylguanidine.*—The following method is based on the work of Arndt and Rosenau (*Ber.*, 1917, **50**, 1261) who condensed benzoylcyanamide with aniline in presence of a little hydrochloric acid to give benzoylphenylguanidine, and of Pierron (*Compt. rend.*, 1910, **151**, 1364) who hydrolysed this to

phenylguanidine. The method was found to be more convenient than that described in G.P. 172,979 (*Chem. Zent.*, 1906, II, 984) which describes the preparation of the nitrate (m. p. 166°) from cyanamide itself.

Benzoylcyanamide (120 g.), *p*-chloroaniline hydrochloride (270 g.), and alcohol (250 c.c.) were mixed, and the clear solution thus obtained was evaporated to dryness on the steam-bath in an open dish. The solid residue was finely ground, stirred for several hours with water (1·5 l.) at room temperature, and the undissolved *N*-benzoyl-*N'*-*p*-chlorophenylguanidine hydrochloride collected and washed with water until free from diazotisable amine. The filter cake was then added to a mixture of sodium hydroxide (410 c.c. of 32%) and water (2 l.) and refluxed with stirring for 20 minutes. The resulting solution was treated with decolorising carbon and filtered hot. After cooling, sodium hydroxide (1300 c.c. of 32%) was added to the filtrate. The oil which was precipitated crystallised on standing. The solid was collected, washed with a little water, and dried (yield, 81%). Crystallisation from benzene gave p-*chlorophenylguanidine* as colourless prisms, m. p. 121° (Found: C, 49·6; H, 4·6; N, 24·0. $C_7H_8N_3Cl$ requires C, 49·5; H, 4·8; N, 24·8%).

Condensation of p-*Chlorophenylguanidine and* 2-*Chloro*-4-*β*-*diethylaminoethylamino*-6-*methylpyrimidine.*—2-Chloro-4-*β*-diethylaminoethylamino-6-methylpyrimidine (4·05 g.) (Part XV, *loc. cit.*) and *p*-chlorophenylguanidine (2·83 g.) were mixed and heated at 110—120° for 18 hours. The mixture was cooled, dissolved in dilute acetic acid, and filtered from a little insoluble matter. Addition of sodium hydroxide precipitated an oil which was extracted with benzene, and the benzene solution was dried (NaOH) and evaporated. Treatment of a portion of the oil with methanolic picric acid gave the dipicrate of 2-*p*-chloroanilino-4-*β*-diethylaminoethylamino-6-methylpyrimidine, identical with an authentic specimen (Curd and Rose, *J.*, 1946, 343) after crystallisation from 2-ethoxyethanol, m. p. and mixed m. p. 218—219°. The rest of the oil was dissolved in alcohol, made just acid to Congo-red with alcoholic hydrochloric acid, and ethyl acetate added. The resulting white precipitate was collected and recrystallised from alcohol–ethyl acetate, giving 2-*p*-chloroanilino-4-*β*-diethylaminoethylamino-6-methylpyrimidine dihydrochloride, m. p. 266° undepressed on admixture with an authentic sample.

Condensation of 4-*Chloro*-2-*β*-*diethylaminoethylamino*-6-*methylpyrimidine with* p-*Chlorophenylguanidine.*—4-Chloro-2-*β*-diethylaminoethylamino-6-methylpyrimidine (4·85 g.) (Part VI, *loc. cit.*) and *p*-chlorophenylguanidine (3·73 g.) were heated at 110—120° with stirring for 22 hours. The cooled melt was dissolved in dilute acetic acid, filtered from a little insoluble matter, and added to excess of dilute sodium hydroxide solution. The precipitated viscous oil was separated by decantation and washed twice with boiling water (30 c.c.). It was then dissolved in dilute hydrochloric acid and the solution evaporated to dryness. Crystallisation of the residue from alcohol gave 4-*p*-chloroanilino-2-*β*-diethylaminoethylamino-6-methylpyrimidine dihydrochloride, m. p. and mixed m. p. 268—269° (Found: N, 16·4; Cl, 24·7; Cl′, 16·2. Calc. for $C_{17}H_{24}N_5Cl,2HCl,1·5\ H_2O$: N, 16·2; Cl, 24·6; Cl′, 16·4%). The corresponding dipicrate crystallised from 2-ethoxyethanol, m. p. 228—229° undepressed on admixture with an authentic specimen (see Part VI) (Found: C, 44·0; H, 4·0; N, 19·5. Calc. for $C_{17}H_{24}N_5Cl,2C_6H_3O_7N_3$: C, 44·0; H, 3·8; N, 19·5%).

The same result was obtained when the two reactants were heated at 150—160° for 17 hours, but there was no reaction at 80° for 22 hours, in acetic acid at 100°, in water at 80° in presence of calcium carbonate as acid-binding agent, at the boil in the presence of chlorobenzene and dilute sodium hydroxide, or at the boil with the addition of 1·1 mols. of hydrochloric acid. With 2·1 mols. of hydrochloric acid and refluxing for 21 hours, the only product which could be isolated was 4-*p*-chloroanilino-2-*β*-diethylaminoethylamino-6-methylpyrimidine. In phenol at 100—110° for 22 hours, 2-*β*-diethylaminoethylamino-4-phenoxy-6-methylpyrimidine appeared to be formed and was isolated as its *dipicrate* which formed yellow crystals from 2-ethoxyethanol, m. p. 194—195° (Found: N, 18·1. $C_{17}H_{24}ON_4,2C_6H_3O_7N_3$ requires N, 18·5%). In boiling xylene (although not in chlorobenzene) in presence of potassium carbonate and copper bronze 4-*p*-chloroanilino-2-*β*-diethylaminoethylamino-6-methylpyrimidine was the only product.

N-p-*Chlorophenyl*-S-*methyl*isothiourea.—*p*-Chlorophenylthiourea (74·6 g.) (Stollé, *J. pr. Chem.*, 1932, **134**, 298) and water (28 c.c.) were mixed into a paste and methyl sulphate (55·2 g., 0·5 mol.) added. On gentle warming a vigorous reaction ensued. When this had subsided the clear solution was refluxed for 1 hour, cooled, and sodium carbonate added to give a faintly alkaline reaction. An oil separated which crystallised almost immediately. It was collected, washed with water, drained well, and recrystallised from methanol (yield, 72%), giving colourless needles, m. p. 83° (Found: C, 47·9; H, 4·2; S, 15·8. $C_8H_9N_2ClS$ requires C, 47·9; H, 4·5; S, 15·95%).

Condensation of N-p-*Chlorophenyl*-S-*methyl*isothiourea *with* 4-*Chloro*-2-*β*-*diethylaminoethylamino*-6-*methylpyrimidine.*—*N*-*p*-Chlorophenyl-*S*-methylisothiourea (4·0 g.) and 4-chloro-2-*β*-diethylaminoethylamino-6-methylpyrimidine (4·85 g.) were stirred and heated at 100—110° for 24 hours. The viscous mixture was dissolved in dilute acetic acid, and the solution filtered, made alkaline with sodium hydroxide, and extracted with benzene. Evaporation of the dried (NaOH) benzene extract left an oil which was dissolved in methanol and sufficient alcoholic hydrochloric acid added to render the solution acid to litmus. Ethyl acetate was then added, and the precipitated hydrochloride collected and crystallised from butanol. It proved to be 4-*p*-chloroanilino-2-*β*-diethylaminoethylamino-6-methylpyrimidine dihydrochloride (Part VI, *loc. cit.*), m. p. and mixed m. p. 264—266°.

2-*Hydroxy*-4-p-*chlorophenylguanidino*-6-*methylpyrimidine* [VII; X = NH·C(:NH)·NH, R = OH].—2-Hydroxy-4-methylthio-6-methylpyrimidine (15·6 g.) (Wheeler and McFarland, *loc. cit.*) and *p*-chlorophenylguanidine (18·65 g.) were boiled in *o*-dichlorobenzene (100 c.c.) for 48 hours. Complete solution was initially obtained and methylthiol evolved, followed at a later stage by the separation of crystalline material. After cooling, the product was collected, washed with *o*-dichlorobenzene, then with alcohol, and dried. Extraction with hot 2N-hydrochloric acid and treatment with carbon gave, on standing, 2-*hydroxy*-4-p-*chlorophenylguanidino*-6-*methylpyrimidine hydrochloride* as colourless crystals, m. p. 198° (decomp.) (Found: C, 43·8; H, 4·6; N, 21·1; Cl′, 10·3. $C_{11}H_{12}ON_5Cl,HCl,H_2O$ requires C, 43·5; H, 4·5; N, 21·1; Cl′, 10·7%).

For the subsequent synthetic work, described below, the crude base, m. p. > 300°, obtained by precipitation of the above 2N-hydrochloric acid extract with ammonia was used.

4-p-*Chlorophenylguanidino-2-β-diethylaminoethylamino-6-methylpyrimidine* {II; X = NH·C(:NH)·NH, R = $[CH_2]_3$·NEt_2}.—(*a*) The above crude hydroxy-compound, finely ground, (10·9 g.) was added, during 15 minutes, to a mixture of chlorobenzene (30 c.c.) and phosphoryl chloride (4·5 c.c.) at 95—100° with stirring. When the addition was complete the mixture was stirred at the same temperature for a further 15 minutes and then poured on to a mixture of ice (200 g.) and sodium hydroxide (30 c.c. of 35%). The crude 2-chloro-4-*p*-chlorophenylguanidino-6-methylpyrimidine, deposited as a gum, was separated and washed with water by decantation. It was then added to a mixture of β-diethylaminoethylamine (6·7 g.), chlorobenzene (30 c.c.), water (30 c.c.), and aqueous sodium hydroxide (17 c.c. of 35%), and the mixture refluxed with stirring for 2 hours. The chlorobenzene and excess of β-diethylaminoethylamine were then removed by steam distillation. The residual undissolved product was separated and extracted with dilute acetic acid, leaving an undissolved residue (see later). The acetic acid extract was treated with decolorising carbon, filtered, and the filtrate run into a mixture of sodium hydroxide (170 c.c. of 15%) and alcohol (150 c.c.) at 75° with stirring. The crystalline precipitate thus obtained was collected, washed with water, and crystallised from alcohol, giving 4-p-*chlorophenylguanidino-2-β-diethylamino-ethylamino-6-methylpyrimidine* (yield, 1·65 g.) as small colourless plates, m. p. 184° (Found: C, 57·1; H, 7·0; N, 25·7; Cl, 9·2. $C_{18}H_{26}N_7Cl$ requires C, 57·5; H, 7·0; N, 26·1; Cl, 9·4%) (4924).

(*b*) 4-*p*-Chlorophenylthioureido-2-β-diethylaminoethylamino-6-methylpyrimidine (1·0 g.) (see below), copper sulphate (pentahydrate, 1·0 g.), and methanolic ammonia (20 c.c. of 18%) were stirred at 40—45° for 4 hours. The mixture was then cooled, acidified with dilute hydrochloric acid, and the excess of copper precipitated with sodium sulphide. After filtration, the solution was poured into ice-cold dilute sodium hydroxide solution, and the precipitated solid collected, washed with water, and dried. Crystallisation from benzene then gave 4-*p*-chlorophenylguanidino-2-β-diethylaminoethylamino-6-methylpyrimidine (yield, 94%), m. p. 183—184°, either alone or admixed with material made by method (*a*).

4-p-*Chlorophenylguanidino-2-γ-diethylaminopropylamino-6-methylpyrimidine*{II; X=NH·C(:NH)·NH, R = $[CH_2]_3$·NEt_2}.—Crude 2-hydroxy-4-*p*-chlorophenylguanidino-6-methylpyrimidine (5·55 g.) was stirred with phosphoryl chloride (3·7 c.c.) at 100° for 30 minutes and then refluxed gently for 15 minutes. The mixture was poured into a mixture of ice and sodium hydroxide solution. The solid chloro-compound formed was broken up, filtered, washed with water, and drained. Without being dried it was heated with γ-diethylaminopropylamine (5·2 g.) at 100° for 1 hour. The mixture was treated with dilute acetic acid, the insoluble material (see below) filtered off, and the filtrate treated with decolorising carbon and again filtered. The filtrate was then added gradually with stirring to a mixture of excess of aqueous sodium hydroxide and alcohol. The resulting precipitate was collected, washed with water, and crystallised from aqueous alcohol, giving 4-p-*chlorophenylguanidino-2-γ-diethylamino-propylamino-6-methylpyrimidine* as minute colourless prisms (yield, 1·25 g.), m. p. 170—171° (Found: C, 58·1; H, 6·8; Cl, 9·7. $C_{19}H_{28}N_7Cl$ requires C, 58·5; H, 7·2; Cl, 9·1%) (4985).

4-p-*Chlorophenylguanidino-2-γ-di-n-butylaminopropylamino-6-methylpyrimidine* {II; X = NH·C(:NH)·NH, R = $[CH_2]_3$·NBu^n_2}.—Crude 2-hydroxy-4-*p*-chlorophenylguanidino-6-methylpyrimidine (7·0 g.) was added during 15 minutes to phosphoryl chloride (20 c.c.) at 70°. The temperature was then raised to 100° and the mixture stirred at this temperature for 15 minutes. Most of the excess of phosphoryl chloride was then removed under diminished pressure and the residue added to ice and ammonia. The precipitated solid was filtered off, washed with water, and added to a mixture of γ-di-*n*-butylaminopropylamine (7·0 g.), chlorobenzene (30 c.c.), water (30 c.c.), and sodium hydroxide (15 c.c. of 35%), and the whole boiled under reflux for 2 hours with stirring. The chlorobenzene and excess of amine were then removed by steam distillation, and the residue collected, washed with water, and extracted with dilute acetic acid. After removal of the insoluble matter by filtration, the acid extract was treated with decolorising carbon and then added to a mixture of dilute sodium hydroxide and alcohol. The solid product on crystallisation from aqueous alcohol gave 4-p-*chlorophenylguanidino-2-γ-di*-n-*butylaminopropylamino-6-methylpyrimidine* (yield, 1·6 g.) as minute colourless prisms, m. p. 168° (Found: N, 22·0; Cl, 8·2. $C_{23}H_{36}N_7Cl$ requires N, 22·0; Cl, 8·0%) (4986).

The material insoluble in dilute acetic acid, from this and the two preceding similar experiments (9·0 g.), was added to phosphoryl chloride (30 c.c.) at 80° during 10 minutes. After being stirred at 100° for 1 hour the mixture was drowned into crushed ice and excess of ammonia. The resulting solid was collected, washed with water, and dried. It was then added to γ-dimethylaminopropylamine (7·4 g.) and the mixture heated at 100—110° with stirring for 1·5 hours. The mass was then dissolved in 5% acetic acid, filtered from insoluble matter, and the filtrate decolorised with charcoal and made alkaline with sodium hydroxide. The oily base was separated, washed with water, and dried. It was then dissolved in alcohol, the solution made acid to Congo-red with alcoholic hydrogen chloride, and ethyl acetate added. The precipitated hydrochloride was filtered off and crystallised from alcohol, m. p. 268—270°, either alone or admixed with authentic 4-*p*-chloroanilino-2-γ-dimethylaminopropylamino-6-methylpyrimidine (Part VI, *loc. cit.*) (Found: N, 17·2; Cl, 26·8. Calc. for $C_{16}H_{22}N_8Cl,2HCl$: N, 17·8; Cl, 27·1%).

4-*Amino-2-β-diethylaminoethylamino-6-methylpyrimidine*.—2-Chloro-4-amino-6-methylpyrimidine (4 g.) (Gabriel and Colman, *Ber.*, 1899, **32**, 2923) and β-diethylaminoethylamine (20 g.) were boiled under reflux for 6 hours. The mixture was then diluted with water (400 c.c.), sodium hydroxide solution (50 c.c. of 35%) added, and the excess of β-diethylaminoethylamine distilled off in steam. The residual mixture was acidified with hydrochloric acid, stirred with decolorising carbon, and filtered. Addition of sodium hydroxide to the filtrate liberated an oil which was extracted with benzene, and the extract dried (KOH) and evaporated. Crystallisation of the residue from benzene–light petroleum (b. p. 60—80°) gave 4-amino-2-β-diethylaminoethylamino-6-methylpyrimidine, m. p. 100—101° identical with material made by the method described in Part XI (*loc. cit.*) (Found: C, 59·1; H, 9·3; N, 31·7. Calc. for $C_{11}H_{21}N_5$: C, 59·2; H, 9·4; N, 31·4%).

4-p-*Chlorophenylthioureido*-2-β-*diethylaminoethylamino*-6-*methylpyrimidine* (II; X = NH·CS·NH, R = $[CH_2]_2$·NEt_2).—4-Amino-2-β-diethylaminoethylamino-6-methylpyrimidine (3·0 g.) and *p*-chlorophenyl *iso*thiocyanate (2·54 g., 1·1 mols.) were heated in boiling xylene (6 c.c.) for 1 hour. The product which separated on cooling was collected, washed with a little xylene, then with benzene, and crystallised from benzene, giving 4-p-*chlorophenylthioureido*-2-β-*diethylaminoethylamino*-6-*methylpyrimidine* (yield, 46%) as practically colourless prisms, m. p. 165—166° (Found: C, 54·5; H, 6·3; N, 21·4; Cl, 9·9; S, 8·5. $C_{18}H_{25}N_6ClS$ requires C, 55·0; H, 6·4; N, 21·4; Cl, 9·1; S, 8·2%).

4-*Amino*-2-δ-*diethylamino*-α-*methylbutylamino*-6-*methylpyrimidine*.—(*a*) 4-Chloro-2-δ-diethylamino-α-methylbutylamino-6-methylpyrimidine (11·0 g.) (Part VI, *loc. cit.*) and alcoholic ammonia (10 c.c. of 13%) were heated in a sealed tube at 200° for 4 hours. The evaporated reaction mixture was dissolved in 2N-hydrochloric acid, the solution made alkaline with sodium hydroxide, and the liberated oil extracted with benzene. Evaporation of the dried (NaOH) extract and distillation of the residue gave the 4-*amino*-compound as a colourless oil (yield, 63%), b. p. 152—156°/0·17 mm. (Found: C, 63·9; H, 10·1. $C_{14}H_{27}N_5$ requires C, 63·5; H, 10·2%).

(*b*) 2-Chloro-4-amino-6-methylpyrimidine (10 g.) and δ-diethylamino-α-methylbutylamine (50 c.c.) were refluxed for 6 hours. Water (1 l.) and sodium hydroxide (200 c.c. of 35%) were added and the mixture steam distilled to remove excess of diamine. The residual oil was separated and purified by dissolution in acid, filtration, and precipitation with sodium hydroxide. The product, isolated with benzene, had b. p. 152—156°/0·17 mm. The *dipicrate* crystallised from alcohol–2-ethoxyethanol as minute yellow prisms, m. p. 138—139° undepressed on admixture with the picrate of material made by method (*a*) (Found: C, 43·2; H, 4·5; N, 21·4. $C_{14}H_{27}N_5.2C_6H_3O_7N_3$ requires C, 43·1; H, 4·6; N, 21·3%).

The product of interaction of this compound with *p*-chlorophenyl *iso*thiocyanate could not be characterised.

Condensation of p-*Chlorophenylguanidine with* 4-*Hydroxy*-2-*methylthio*-6-*methylpyrimidine*.—(*a*) *p*-Chlorophenylguanidine (3·39 g.) and 4-hydroxy-2-methylthio-6-methylpyrimidine (3·12 g.) (Wheeler and Merriam, *Amer. Chem. J.*, 1903, **29**, 478) were stirred and heated at 160—170° for 24 hours. After cooling, the hard mass was broken up and boiled with 2-ethoxyethanol. The undissolved solid was filtered off, washed with alcohol, and dried, giving crude 4-hydroxy-2-*p*-chlorophenylguanidino-6-methylpyrimidine [VIII; X = NH·C(:NH)·NH, R = Cl, R′ = OH], m. p. 276° (yield, 28%). After crystallisation from nitrobenzene the material was identical with that described in Part IV (*loc. cit.*), m. p. and mixed m. p. 288—289°.

(*b*) *p*-Chlorophenylguanidine (8·5 g.), 4-hydroxy-2-methylthio-6-methylpyrimidine (7·8 g.), and *o*-dichlorobenzene (30 c.c.) were boiled under reflux for 21 hours. Methylthiol was evolved, and the solution, initially clear, deposited solid. After cooling, this was collected, washed with methanol, and dried, m. p. 252—258° (yield, 5·65 g.). Without further purification the finely powdered solid was added during 10 minutes, with stirring, to phosphoryl chloride (15 c.c.) preheated to 90—95°. The mixture was then refluxed for 15 minutes and the excess of phosphoryl chloride removed under diminished pressure. The residue was added to ice and water (100 g.). The resulting gummy solid, separated by decantation, was dissolved in acetic acid (25 c.c.) and the solution added to water (100 c.c.). The resulting precipitate was filtered off, washed with water, and dried. Crystallisation from alcohol gave 4-chloro-2-*p*-chloroanilino-6-methylpyrimidine (VIII; X = NH, R = R′ = Cl), m. p. 127—128° alone or mixed with authentic material (Part I, *J.*, 1946, 343). The above acetic acid filtrate was made alkaline with ammonia and the precipitated product collected, washed with water, and dried. Crystallisation from acetone gave a product, m. p. 180—182°, which proved to be 4-chloro-2-*p*-chlorophenylguanidino-6-methylpyrimidine [VIII; X = NH·C(:NH)·NH, R = R′ = Cl] (mixed m. p. 180—182°).

Condensation of p-*Anisylguanidine with* 4-*Hydroxy*-2-*methylthio*-6-*methylpyrimidine*.—p-Anisylguanidine (4·12 g.) (prepared by condensing *p*-anisidine with *S*-methyl*iso*thiourea sulphate; recipe kindly supplied by Sir Robert Robinson) and 4-hydroxy-2-methylthio-6-methylpyrimidine (3·9 g.) were finely ground together and heated at 160—170° for 6 hours. The cooled melt was lixiviated with warm alcohol (15 c.c.) and the resulting white solid collected, washed with alcohol, and dried, m. p. 247—248°. Crystallisation from 2-ethoxyethanol gave 4-hydroxy-2-*p*-anisylguanidino-6-methylpyrimidine [VIII; X = NH·C(:NH)·NH, R = OMe, R′ = OH], m. p. 253° alone or admixed with material made by condensation of *p*-anisyldiguanide and ethyl acetoacetate (Part IV, *loc. cit.*).

4-*Hydroxy*-2-*guanidino*-6-*methylpyrimidine* [X; R = C(:NH)·NH_2].—2-Cyanoamino-4-hydroxy-6-methylpyrimidine (45 g.) (X; R = CN) (Pohl, *loc. cit.*), ammonia (21 c.c., *d* 0·88), ammonium chloride (16 g.), and 2-ethoxyethanol (180 c.c.) were stirred at 140—150° in an autoclave for 21 hours. After cooling, the solid product was collected and washed with 2-ethoxyethanol. The greyish crystals were stirred with water (1 l.) and ammonia (15 c.c., *d* 0·88) for ½ hour, filtered off, and washed with water and then with water containing a few drops of acetic acid. The resulting yellowish product (yield, 61%) had m. p. 303° (decomp.). The m. p. was not raised by dissolving in boiling 30% acetic acid, filtering, and neutralising the hot solution with sodium hydroxide (Found: C, 42·9; H, 5·5. $C_6H_9ON_5$ requires C, 43·1; H, 5·4%. Nitrogen determinations were unsatisfactory).

Condensation of 4-*Hydroxy*-2-*guanidino*-6-*methylpyrimidine with* p-*Chloroaniline*.—The preceding compound (6·7 g.) and *p*-chloroaniline hydrochloride (6·6 g.) in water (50 c.c.) were stirred and boiled under reflux for 60 hours. After cooling, the insoluble material was filtered off and stirred with 2N-sodium hydroxide to remove unchanged material. The insoluble portion was dissolved in boiling 3N-hydrochloric acid, the solution filtered hot, and the filtrate made alkaline with sodium hydroxide. The precipitated product was collected, washed with water, dried, and crystallised from nitrobenzene giving 4-hydroxy-2-*p*-chlorophenylguanidino-6-methylpyrimidine, m. p. and mixed m. p. 285—287° (Found: N, 25·0. Calc. for $C_{12}H_{12}ON_5Cl$: N, 25·2%).

4-p-*Chlorophenylthioureido*-6-β-*diethylaminoethylamino*-2-*methylpyrimidine* (III; X = NH·CS·NH, R = $[CH_2]_2$·NEt_2).—4-Amino-6-β-diethylaminoethylamino-2-methylpyrimidine (11·3 g.) (Hull, Lovell,

Openshaw, Payman, and Todd, *J.*, 1946, 357), *p*-chlorophenyl *iso*thiocyanate (9·45 g.), and toluene (20 c.c.) were boiled under reflux for 20 minutes. After cooling, the precipitated product was collected, washed with benzene, dried, and crystallised from light petroleum (b. p. 120—140°), giving the *thiourea* as pale fawn needles, m. p. 169° (Found: N, 21·4; Cl, 9·1; S, 7·6. $C_{18}H_{25}N_6ClS$ requires N, 21·4; Cl, 9·1; S, 8·1%) (5227).

4-p-*Chlorophenylguanidino*-6-*β*-*diethylaminoethylamino*-2-*methylpyrimidine* {III; X = NH·C(:NH)·NH, R = $[CH_2]_3$·NEt_2}.—The above thioureido-compound (5·0 g.), mercuric oxide (5·0 g.), and methanolic ammonia (90 c.c. of 18%) were stirred at 30—40° for 4·5 hours and the mixture then treated with dilute hydrochloric acid and sodium sulphide. The mercuric sulphide was filtered off and the filtrate added dropwise to ice-cold 2N-sodium hydroxide with stirring. The solid thus precipitated was filtered off, washed with water, and dried (yield, 94%). Crystallised from light petroleum (b. p. 120—140°), 4-p-*chlorophenylguanidino*-6-*β*-*diethylaminoethylamino*-2-*methylpyrimidine* was obtained as colourless needles, m. p. 154—155° (Found: C, 57·0; H, 6·2; N, 25·7. $C_{18}H_{26}N_7Cl$ requires C, 57·5; H, 6·9; N, 26·1%) (5236).

4-p-*Chlorophenylthioureido*-6-*γ*-*diethylaminopropylamino*-2-*methylpyrimidine* (III; X = NH·CS·NH, R = $[CH_2]_3$·NEt_2).—4-Amino-6-*γ*-diethylaminopropylamino-2-methylpyrimidine (10 g.) (Hull *et al.*, *loc. cit.*) and *p*-chlorophenyl *iso*thiocyanate (7·85 g.) in toluene (20 c.c.) were refluxed for 20 minutes. The crystalline material which separated on cooling was collected, washed first with toluene then with benzene, and dried (yield, 59%). Crystallisation from benzene–xylene gave 4-p-*chlorophenylthioureido*-6-*γ*-*diethylaminopropylamino*-2-*methylpyrimidine* as light fawn plates, m. p. 187° (Found: C, 56·2; H, 6·7; N, 20·7; Cl, 8·9; S, 8·2. $C_{19}H_{27}N_6ClS$ requires C, 56·2; H, 6·7; N, 20·7; Cl, 8·7; S, 7·9%) (5218).

4-p-*Chlorophenylguanidino*-6-*γ*-*diethylaminopropylamino*-2-*methylpyrimidine* {III; X = NH·C(:NH)·NH, R = $[CH_2]_3$·NEt_2}.—The preceding compound (5·0 g.) was stirred with mercuric oxide (5·0 g.) and methanolic ammonia (70 c.c. of 18%) at room temperature for 12 hours and then at 36—40° for 3 hours. The mixture was worked up as described above for the corresponding *β*-diethylaminoethylamino-compound (yield, 93%). 4-p-*Chlorophenylguanidino*-6-*γ*-*diethylaminopropylamino*-2-*methylpyrimidine* crystallised from light petroleum as minute colourless prisms, m. p. 112—113° (Found: C, 58·2; H, 7·0; Cl, 9·1. $C_{19}H_{28}N_7Cl$ requires C, 58·5; H, 7·2; Cl, 9·1%) (5243).

4-Amino-6-*δ*-diethylamino-*α*-methylbutylamino-2-methylpyrimidine, prepared by the method of Hull *et al.* (*loc. cit.*), was obtained as a colourless oil, b. p. 180—182°/0·13 mm. It gave a *dipicrate* which crystallised from methanol–2-ethoxyethanol, m. p. 139—141° (Found: C, 42·8; H, 4·4; N, 20·8. $C_{14}H_{27}N_5,2C_6H_3O_7N_3$ requires C, 43·2; H, 4·6; N, 21·3%). Attempts to condense this aminopyrimidine with *p*-chlorophenyl *iso*thiocyanate led to a product which could not be characterised.

2-N^1-p-*Chlorophenyl*-N^3-*methylguanidino*-N^3-4-*β*-*diethylaminoethylamino*-6-*methylpyrimidine* {I; X = NH·C(:NMe)·NH, R = $[CH_2]_3$·NEt_2}.—2-*p*-Chlorophenylthioureido-4-*β*-diethylaminoethylamino-6-methylpyrimidine (4·0 g.) (preceding paper), aqueous methylamine (25 c.c. of 22%), and mercuric oxide (4·0 g.) were added consecutively to alcohol (40 c.c.) with stirring. The mixture darkened rapidly and was stirred at 50—55° for 2 hours. After cooling, the mixture was acidified with hydrochloric acid, excess of sodium sulphide added, and the mercuric sulphide filtered off and washed with water. The filtrate and washings were added to excess of cold 2N-sodium hydroxide, and the precipitated solid collected, washed with water, and dried in a vacuum. It was then dissolved in a slight excess of alcoholic hydrogen chloride and ethyl acetate added. The precipitated *trihydrochloride* was filtered off, dried, and recrystallised from alcohol–ethyl acetate, giving a colourless microcrystalline powder, m. p. 181—182° (Found: C, 44·1; H, 6·2; N, 18·7; Cl, 27·0. $C_{19}H_{28}N_7Cl,3HCl,H_2O$ requires C, 44·1; H, 6·4; N, 18·95; Cl, 27·5%) (5165). The *base*, liberated from the hydrochloride with sodium hydroxide, crystallised from light petroleum (b. p. 120—140°) as minute colourless prisms, m. p. 95·5° (Found: C, 58·1; H, 7·2; N, 25·4; Cl, 9·5. $C_{19}H_{28}N_7Cl$ requires C, 58·5; H, 7·2; N, 25·2; Cl, 9·1%).

2-N^1-p-*Chlorophenyl*-N^3-*ethylguanidino*-N^3-4-*β*-*diethylaminoethylamino*-6-*methylpyrimidine* {I; X = NH·C(:NEt)·NH, R = $[CH_2]_3$·NEt_2}, prepared by using ethylamine in place of methylamine, crystallised from light petroleum (b. p. 100—120°) as minute colourless prisms, m. p. 92° (Found: C, 60·1; H, 7·1; N, 23·7; Cl, 8·8. $C_{20}H_{30}N_7Cl$ requires C, 59·5; H, 7·5; N, 24·3; Cl, 8·8%) (5324).

2-N^1-p-*Chlorophenyl*-N^3-n-*butylguanidino*-N^3-4-*β*-*diethylaminoethylamino*-6-*methylpyrimidine* {I; X = NH·C(:NBu^n)·NH, R = $[CH_2]_3$·NEt_2}, prepared by using *n*-butylamine, crystallised from aqueous methanol in colourless needles, m. p. 85—87° (Found: C, 58·4; H, 8·1. $C_{22}H_{34}N_7Cl,H_2O$ requires C, 58·8; H, 8·0%). The *dihydrochloride* crystallised from alcohol–ethyl acetate as a colourless microcrystalline powder, m. p. 168—169° (Found: C, 50·9; H, 7·3; N, 19·0; Cl, 20·3. $C_{22}H_{34}N_7Cl,2HCl,H_2O$ requires C, 50·6; H, 7·3; N, 18·8; Cl, 20·4%) (5369).

2-N^1-p-*Chlorophenyl*-N^3-*methylguanidino*-N^3-4-*γ*-*diethylaminopropylamino*-6-*methylpyrimidine* {I; X = NH·C(:NMe)·NH, R = $[CH_2]_3$·NEt_2}.—2-*p*-Chlorophenylthioureido-4-*γ*-diethylaminopropylamino-6-methylpyrimidine (4·0 g.) (preceding paper), mercuric oxide (4·0 g.), alcohol (45 c.c.), 2-ethoxyethanol (20 c.c.), and methylamine (25 c.c. of 21%) were stirred at 50—55° for 4 hours. The mixture was acidified with hydrochloric acid, excess of sodium sulphide added, and the mixture filtered. The filtrate was drowned into excess of ice-cold sodium hydroxide and the sticky base, washed by decantation, dried in a vacuum. It was then dissolved in alcoholic hydrochloric acid and ethyl acetate added. The solid *trihydrochloride* was filtered off and crystallised from alcohol–ethyl acetate, giving a colourless microcrystalline powder, m. p. 175—176° (Found: C, 44·5; H, 6·2; N, 18·1; Cl, 25·5. $C_{20}H_{30}N_7Cl$, 3HCl,1·5H_2O requires C, 44·5; H, 6·7; N, 18·3; Cl, 26·3%) (5334).

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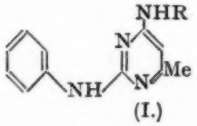
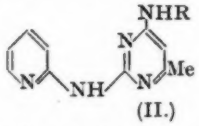
122. *Synthetic Antimalarials. Part XXVI. Pyridyl- and Pyrimidyl-aminopyrimidines.*

By F. H. S. Curd, W. Graham, and F. L. Rose.

Several pyrimidylamino- and pyridylamino-pyrimidines analogous to the anilinopyrimidines of earlier parts in this series of papers have been prepared for testing as antimalarial agents.

Some of the earlier contributions to this series of papers have been concerned with the chemical modification of substances of type (I), initially described in Part I (Curd and Rose, *J.*, 1946, 343),


(I.)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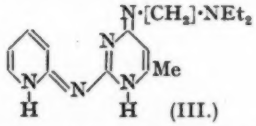
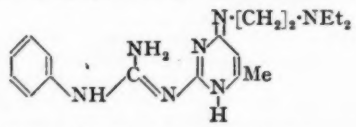
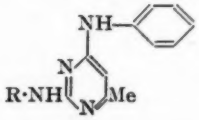

(III.)

in which the benzene ring was variously substituted and the R group was of the alkylaminoalkyl class. In all the modifications of this particular type, the benzene ring has been retained intact, although in two it has been incorporated into other cyclic systems, namely, naphthalene (Part V, Curd, Raison, and Rose, *J.*, 1946, 366) and quinoline (Part XXII, Curd, Graham, Richardson, and Rose, *J.*, to appear). Although the introduction of quinoline into the molecule provided analogues of (I) carrying a heterocyclic system attached to position 2 of the pyrimidine ring, yet the linkage to the quinoline nucleus was through amino-groups in positions 5, 6, and 8 of the latter; that is, the resulting substances were still substituted anilinopyrimidines. It appeared to be of interest therefore to investigate the preparation of analogues of (I) in which the heterocyclic grouping was directly substituted into the 2-amino-group of the pyrimidine. The most closely related compounds would be those in which the benzene ring was replaced either by pyridine or by a second pyrimidine nucleus. It was appreciated that antimalarial activity was most likely to be associated with those variants in which the new ring system carried substituents of the same class and in the same relative position as those which induce activity in the anilinopyrimidines, for example, *para* chlorine, but, because of the difficulties involved in the preparation of many such derivatives, use was made in the initial experiments of less favourable, but more readily available structures. Thus, 4-hydroxy-2-methylthio-6-methylpyrimidine (Wheeler and Merriam, *Amer. Chem. J.*, 1903, **29**, 478) and 2-aminopyridine were condensed to form 2-(2′-*pyridylamino*)-4-*hydroxy*-6-*methylpyrimidine* which was converted into 4-*chloro*-2-(2′-*pyridylamino*)-6-*methylpyrimidine* with phosphoryl chloride. This chloropyrimidine was condensed with β-diethylaminoethylamine at 130° to give 2-(2′-*pyridylamino*)-4-β-*diethylamino-ethylamino*-6-*methylpyrimidine* (as II). The possible significance of prototropy in relation to the antimalarial activity of type (I) has been discussed in previous communications in this series (see Part XII, *J.*, 1947, 154). Structure (II, R = $C_2H_4{\cdot}NEt_2$) possesses additional possibilities of this kind; for example, the form (III) which is analogous in some respects to one of the hypothetical tautomers (IV) of the 2-arylguanidino-4-aminoalkylamino-6-methylpyrimidine type described in Part IV (*J.*, 1946, 362), of which several members were notable for their marked antimalarial activity. Against that, it was appreciated that (IV) was not the particular tautomer considered to be biologically significant in this type since the conjugation within the molecule was only partial (see Part XII).

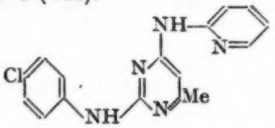
(IV.) 

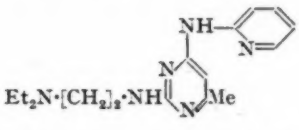

(V.)

In addition to the tautomeric features associated with 2-aminopyridine, it was considered that this basic structure might effectively replace the basic alkyl side chain of (I) and of its active isomer (V). For the preparation of substances (II, R = substituted Ph) corresponding to the latter type, the 4-chloro-2-(2′-pyridylamino)-6-methylpyrimidine described above was brought into reaction with *p*-nitroaniline and *p*-chloroaniline in boiling dilute hydrochloric acid solution to give (II, R = *p*-$C_6H_4{\cdot}NO_2$) and (II, R = *p*-C_6H_4Cl) respectively.

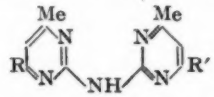
2-*p*-*Chloroanilino*-4-(2′-*pyridylamino*)-6-*methylpyrimidine* (VI), bearing the same relation to (I), was prepared by interaction of 2-aminopyridine and 4-chloro-2-*p*-chloroanilino-6-methylpyrimidine (Curd and Rose, *J.*, 1946, 349). 2-Aminopyridine and 4-chloro-2-β-diethyl-

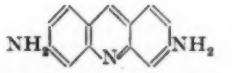
aminoethylamino-6-methylpyrimidine (Curd, Davis, Owen, Rose, and Tuey, *J.*, 1946, 373) similarly gave (VII).

(VI.) 

 (VII.)

Unsuccessful attempts were made to condense 2-amino-4 : 6-dimethylpyrimidine in the same way with 4-chloro-2-*p*-chloroanilino-6-methylpyrimidine and 4-chloro-2-β-diethylaminoethylamino-6-methylpyrimidine, to give the dipyrimidylamines analogous to (VI) and (VII), but the preparation of isomeric (VIII, R = Me, R′ = NH·[CH_2]$_2$·NEt_2) was achieved by an indirect method involving total synthesis of the added pyrimidine ring. For this purpose 4-hydroxy-2-guanidino-6-methylpyrimidine (Crowther, Curd, and Rose, Part XXV, previous paper) prepared by the original method from 2-cyanoamino-4-hydroxy-6-methylpyrimidine and

(VIII.) 

 (IX.)

ammonia, and also by a new synthesis from diguanide and ethyl acetoacetate, was condensed in boiling acetic acid solution with acetylacetone to give *6′-hydroxy-4 : 4′ : 6-trimethyl-2 : 2′-dipyrimidylamine*. This with phosphoryl chloride gave the corresponding 6′-chloro-derivative which was then heated with β-diethylaminoethylamine to form (VIII, R = Me, R′ = NH·[CH_2]$_2$·NEt_2). The same chloropyrimidine served for the preparation of the simpler substance *6′-dimethylamino-4 : 4′ : 6-trimethyl-2 : 2′-dipyrimidylamine* by interaction with dimethylamine.

Condensation of 4-hydroxy-2-guanidino-6-methylpyrimidine with a further molecule of ethyl acetoacetate gave *6 : 6′-dihydroxy-4 : 4′-dimethyl-2 : 2′-dipyrimidylamine*. This, converted into the corresponding 6 : 6′-dichloropyrimidine by treatment with phosphoryl chloride, followed by reaction with dimethylamine and *iso*propylamine, gave (VIII, R = R′ = NMe_2) and (VIII, R = R′ = $NHPr^{\beta}$); these could be regarded as structurally related to 2 : 8-diaminoacridine (IX, "proflavine"), and for this reason they were examined by our colleague Dr. A. R. Martin for antibacterial activity. They were inactive, however, against the several organisms used in the test.

The final amino-derivatives were examined for antimalarial activity by our colleague, Dr. D. G. Davey, using chicks infected with *P. gallinaceum*. They were all inactive.

Experimental.

2-(2′-Pyridylamino)-4-hydroxy-6-methylpyrimidine.—The solid obtained by heating at 150—160° for 100 hours a mixture of 2-aminopyridine (14 g.) and 4-hydroxy-2-methylthio-6-methylpyrimidine (Wheeler and Merriam, *loc. cit.*) (12 g.) was ground, heated at 100° under diminished pressure to remove unchanged 2-aminopyridine, and extracted with a little boiling benzene. The undissolved *hydroxypyrimidine* gave colourless fine needles, m. p. 172—173°, from methanol–benzene (Found : C, 59·6; H, 5·2; N, 27·9. $C_{10}H_{10}ON_4$ requires C, 59·4; H, 4·95; N, 27·7%). After crystallisation twice from water the compound had m. p. 205—207° (Found : C, 59·3; H, 4·8; N, 27·5%), but it reverted to the lower-melting form after several recrystallisations from benzene.

4-Chloro-2-(2′-pyridylamino)-6-methylpyrimidine.—The above hydroxypyrimidine (11 g.) and phosphoryl chloride (45 c.c.) were heated for 4 hours in an oil-bath kept at 115—120°. Excess of phosphoryl chloride was removed under diminished pressure at 100°, the residue cooled, added to ice, and the precipitated solid dissolved in hydrochloric acid. Addition of ammonia gave the *chloropyrimidine* which after being washed and dried in a vacuum formed colourless prismatic rhombs (8·9 g.), m. p. 199—201°, from benzene (Found : C, 54·8; H, 4·2. $C_{10}H_9N_4Cl$ requires C, 54·5; H, 4·1%).

2-(2′-Pyridylamino)-4-β-diethylaminoethylamino-6-methylpyrimidine (II, R = C_2H_4·NEt_2) (6371).—The chloropyrimidine (3 g.) and β-diethylaminoethylamine (2·8 c.c.) were stirred for 10 hours at 130°. The melt was cooled, dissolved in dilute hydrochloric acid, made alkaline with sodium hydroxide, and the oil extracted into chloroform. The chloroform layer was washed with water, extracted with several lots of 5% acetic acid, and the acid extract basified with sodium hydroxide. The precipitated oil was re-extracted into chloroform, washed with water, dried (Na_2SO_4), and the solvent distilled off. The residual oil was converted into the *dihydrochloride* by evaporating to dryness a solution in dilute hydrochloric acid, and after repeated crystallisation from ether–ethanol formed hygroscopic colourless micro-needles (3 g.), m. p. 150°, resolidifying and melting at 239—241° (Found : C, 45·6; H, 7·2; N, 19·6; Cl, 17·2. $C_{16}H_{24}N_6$,2HCl,2·5H_2O requires C, 45·9; H, 7·4; N, 20·1; Cl, 17·0%).

4-p-Nitroanilino-2-(2′-pyridylamino)-6-methylpyrimidine (II, R = *p*-C_6H_4·NO_2) (6373).—The solution obtained by boiling the above chloropyrimidine (2·85 g.), *p*-nitroaniline (1·78 g.), concentrated hydrochloric acid (1·5 c.c.), and water (15 c.c.), rapidly deposited a yellow solid. After 1 hour more

water (10 c.c.) and hydrochloric acid (1·5 c.c.) were added, and refluxing was continued for a further 1 hour. The precipitated *dihydrochloride* crystallised from 2-ethoxyethanol in fine yellow needles (4 g.), decomposing above 320° (Found: C, 47·3; H, 4·8; N, 20·5; Cl, 18·6. $C_{16}H_{14}O_2N_6$,2HCl,0·5H_2O requires C, 47·5; H, 4·3; N, 20·8; Cl, 17·6%).

4-p-*Chloroanilino*-2-(2′-*pyridylamino*)-6-*methylpyrimidine* (II, R = *p*-C_6H_4Cl) (6372).—Similarly prepared from the chloropyrimidine (2·9 g.), *p*-chloroaniline (1·7 g.), concentrated hydrochloric acid (1·45 c.c.), and water (15 c.c.), this formed a *dihydrochloride* which crystallised from dilute hydrochloric acid in colourless needles (4 g.), m. p. 268—270° (Found: C, 50·5; H, 4·15; N, 18·1; Cl, 27·4. $C_{16}H_{14}N_5Cl$,2HCl requires C, 49·9; H, 4·2; N, 18·2; Cl, 27·7%).

2-p-*Chloroanilino*-4-(2′-*pyridylamino*)-6-*methylpyrimidine* (VI) (6047).—The melt obtained by stirring for 10 hours at 125—135° a mixture of 4-chloro-2-*p*-chloroanilino-6-methylpyrimidine (Curd and Rose, *loc. cit.*) (16 g.) and 2-aminopyridine (7·9 g.) was cooled, dissolved in concentrated hydrochloric acid, treated with water, and left overnight. Extraction with hot ethanol of the crystalline precipitate left the *dihydrochloride* which recrystallised from dilute hydrochloric acid in colourless needles (4·5 g.), m. p. 284—287° (Found: C, 49·9; H, 4·2; N, 18·3; Cl, 27·5. $C_{16}H_{14}N_5Cl$,2HCl requires C, 49·9; H, 4·2; N, 18·2; Cl, 27·7%). The dihydrochloride with sodium hydroxide gave the free *base* which formed a colourless micro-crystalline powder from benzene, m. p. 143° (Found: C, 61·1; H, 4·6; N, 22·1. $C_{16}H_{14}N_5Cl$ requires C, 61·6; H, 4·5; N, 22·45%).

4-(2′-*Pyridylamino*)-2-β-*diethylaminoethylamino*-6-*methylpyrimidine* (VII) (6046).—The solution from refluxing for 4 hours a mixture of 4-chloro-2-β-diethylaminoethylamino-6-methylpyrimidine (5·5 g.) (Curd, Davis, Owen, Rose, and Tuey, *loc. cit.*), 2-aminopyridine, 10N-hydrochloric acid (2·5 c.c.), and water (25 c.c.), gave an oil on addition of sodium hydroxide. This was worked up as described above for (II, R = C_2H_4·NEt_2) and converted into the *dihydrobromide* from which excess of water and hydrobromic acid were removed by repeated evaporation to dryness with ethanol–benzene. Repeated crystallisation from ethanol–ether gave hygroscopic colourless needles (2·5 g.) m. p. 150° (efferv.) (Found: C, 36·6; H, 6·2; N, 15·7; Br, 29·7. $C_{16}H_{24}N_6$,2HBr,3·5H_2O requires C, 36·6; H, 6·3; N, 16·0; Br, 30·45%).

4-*Hydroxy*-2-*guanidino*-6-*methylpyrimidine*.—Diguanide sulphate (43·4 g.) was dissolved with stirring in ethanol (50 c.c.) and 11N-sodium hydroxide (40 c.c.), ethyl acetoacetate (28·6 g.) added, and the mixture kept for 48 hours at laboratory temperature. Extraction of the precipitated solid with hot ethanol, then cold water, gave 4-hydroxy-2-guanidino-6-methylpyrimidine (26 g.), m. p. 302—304° (Found: C, 42·6; H, 5·5. Calc. for $C_6H_9ON_5$: C, 43·1; H, 5·4%), identical with that prepared by the method of Crowther, Curd, and Rose (Part XXV, *loc. cit.*).

6′-*Hydroxy*-4 : 4′ : 6-*trimethyl*-2 : 2′-*dipyrimidylamine*.—4-Hydroxy-2-guanidino-6-methylpyrimidine (11·6 g.), acetylacetone (15 c.c.), and acetic acid (60 c.c.), refluxed for 8 hours, gave on dilution with water and addition of ammonia the *product* (13·8 g.) which formed colourless prisms from butanol, m. p. 266—267° (Found: C, 56·8; H, 6·05; N, 29·9. $C_{11}H_{13}ON_5$ requires C, 57·1; H, 5·7; N, 30·3%).

6′-*Chloro*-4 : 4′ : 6-*trimethyl*-2 : 2′-*dipyrimidylamine*.—The above hydroxypyrimidine (8 g.) and phosphoryl chloride (16 c.c.), after being heated at 100° for ½ hour and added to ice and dilute ammonia, gave the solid *product* which, after being dried in a vacuum over sodium hydroxide (yield 7 g.), formed colourless prisms from acetone, m. p. 172—173° (Found: C, 52·9; H, 4·95; N, 27·45. $C_{11}H_{12}N_5Cl$ requires C, 52·8; H, 4·8; N, 28·0%).

6′-β-*Diethylaminoethylamino*-4 : 4′ : 6-*trimethyl*-2 : 2′-*dipyrimidylamine* (VIII, R = Me, R′ = NH·C_2H_4·NEt_2) (3952).—The above chloropyrimidine (4·5 g.) and β-diethylaminoethylamine (10 c.c.) were heated for 1½ hours in an oil-bath kept at 130—140°. After removal of the excess of amine under diminished pressure at 100°, the residue was taken up in dilute acetic acid, and the oil obtained by adding sodium hydroxide was extracted into ether. The solvent was distilled off and the gummy residue dissolved in sufficient N-hydrochloric acid to give a faintly acid solution. Addition of sodium iodide (15 g.) precipitated the *dihydriodide* which, after recrystallisation from water (yield 4·3 g.), had m. p. 246—252°, and after further recrystallisation from ethanol formed pale yellow prisms, m. p. 247—250° (Found: C, 33·9; H, 5·7; N, 15·8. $C_{17}H_{27}N_7$,2HI,H_2O requires C, 33·8; H, 5·15; N, 16·2%).

6′-*Dimethylamino*-4 : 4′ : 6-*trimethyl*-2 : 2′-*dipyrimidylamine* (6541).—The above chloropyrimidine (9·6 g.), dimethylamine (27 c.c. of 25% solution in water), and 2-ethoxyethanol (30 c.c.) were heated in a pressure bottle for 18 hours at 100°. The mixture was diluted with water (250 c.c.), made acid with acetic acid, filtered, and the filtrate evaporated to dryness. The residue was dissolved in water (50 c.c.), charcoaled, and potassium bromide (5 g.) added as a saturated solution. The precipitated *hydrobromide* was collected; after being twice recrystallised from ethanol, it formed colourless needles (7·7 g.), m. p. 288—290° (Found: C, 43·0; H, 6·05; N, 23·4; Br, 22·2. $C_{13}H_{18}N_6$,HBr,1·5H_2O requires C, 42·6; H, 6·0; N, 22·95; Br, 21·85%).

6 : 6′-*Dihydroxy*-4 : 4′-*dimethyl*-2 : 2′-*dipyrimidylamine* (VIII, R = R′ = OH).—4-Hydroxy-2-guanidino-6-methylpyrimidine (8·4 g.), ethyl acetoacetate (9·6 g.), and sodium (4·6 g.) dissolved in methanol (150 c.c.) were mixed and refluxed for 16 hours. The precipitate which had formed dissolved on adding water (250 c.c.). The solution was treated with charcoal and made acid with acetic acid. The crude *product* (10·3 g.), which was precipitated, was taken up in dilute ammonia, filtered from a little insoluble solid, and reprecipitated with acetic acid. It was very sparingly soluble in the common organic solvents, melted with decomposition above 330°, and was used in the next stage of the reaction series without further treatment (Found: C, 48·05; H, 4·95; N, 27·45. $C_{10}H_{11}O_2N_5$,H_2O requires C, 47·8; H, 5·2; N, 27·9%).

6 : 6′-*Dichloro*-4 : 4′-*dimethyl*-2 : 2′-*dipyrimidylamine* (VIII, R = R′ = Cl).—This *compound* was prepared from the dihydroxypyrimidine (12 g.) and phosphoryl chloride (20 c.c.) by heating for 2 hours at 100° and adding to ice and dilute sodium hydroxide. It formed pale yellow prisms (9·4 g.) from toluene, m. p. 178—179° (Found: C, 44·85; H, 3·55; N, 25·8. $C_{10}H_8N_5Cl_2$ requires C, 44·45; H, 3·3; N, 25·9%).

6 : 6′-*Bisdimethylamino*-4 : 4′-*dimethyl*-2 : 2′-*dipyrimidylamine* (VIII, R = R′ = NMe_2) (6558).—Prepared by the method used for the 6′-dimethylamino-derivative described above, using the 6 : 6′-

dichloropyrimidine (10·5 g.), dimethylamine (40 c.c. of a 25% solution in water), and 2-ethoxyethanol (30 c.c.), precipitating the crude product from a clarified solution in dilute hydrochloric acid with sodium hydroxide, and crystallising from toluene, this *compound* formed colourless needles, m. p. 155—156°, which retained toluene after ½ hour in a vacuum at 100° (Found: C, 60·75; H, 7·2; N, 31·3. $C_{14}H_{21}N_7,\frac{1}{2}C_7H_8$ requires C, 61·0; H, 7·4; N, 31·6%).

6 : 6′-*Diisopropylamino*-4 : 4′-*dimethyl*-2 : 2′-*dipyrimidylamine* (VIII, R = R′ = NHPr$^\beta$) (5141).—Similarly prepared from the dichloropyrimidine (2·7 g.) and *iso*propylamine (2·5 c.c.), this *compound* formed colourless prisms from toluene, m. p. 226—227° (Found: C, 60·4; H, 7·95; N, 30·8. $C_{16}H_{25}N_7$ requires C, 60·9; H, 7·95; N, 31·1%).

This research was carried out under a wartime collaborative agreement between the Medical Research Council and Imperial Chemical Industries Ltd. The authors desire to express their thanks to Professor J. W. Cook, F.R.S., and Dr. T. S. Stevens for their interest in the work. One of them (W. G.) gratefully acknowledges the receipt of a grant from the Medical Research Council.

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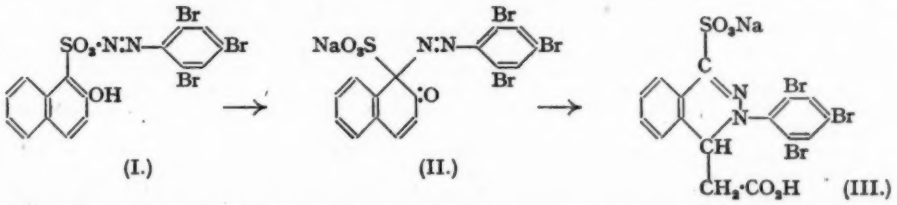
123. *A Reaction of Diazosulphonates derived from β-Naphthol-1-sulphonic Acid. Part XXIV. The Phthalazine Reaction with Bases not containing a Nitro-group. Derivatives of Halogenobenzene-2-naphthol-1-diazosulphonates.**

By A. T. PETERS, G. T. PRINGLE, and (the late) F. M. ROWE.

In Part I of this Series (*J.*, 1926, 692), it was stated that the only diazosulphonates not containing a nitro-group which are convertible into phthalazine derivatives are those derived from 4-aminoazobenzene. It is now shown that the reaction is more general, and phthalazine compounds are obtainable from 2′ : 4′ : 6′-tribromo- and 3′- and 4′-chloro-benzene-2-naphthol-1-diazosulphonate. The derived 1-*hydroxy*-3-*halogenophenyl*-3 : 4-*dihydrophthalazine*-4-*acetic acids* show similar reactions to those of other analogues in this series, but several anomalies are noted.

CONVERSION of 2′ : 4′ : 6′-tribromobenzene-2-naphthol-1-diazosulphonate (I) into the 1-(2′ : 4′ : 6′-tribromobenzeneazo)-β-naphthaquinone-1-sulphonate (II) is slow, but is accelerated by alcohol at 40°, as also is the subsequent action of sodium hydroxide on the latter to form *sodium hydrogen* 3-(2′ : 4′ : 6′-*tribromophenyl*)-3 : 4-*dihydrophthalazine*-1-*sulphonate*-4-*acetate* (III). No trace of

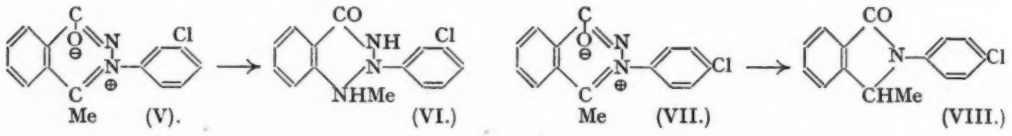


sodium benzaldehyde 2′ : 4′ : 6′-tribromophenylhydrazone-ω-sulphonate-2-β-acrylic acid was detected. Acid hydrolysis of the above sodium salt furnished 1-*hydroxy*-3-(2′ : 4′ : 6′-*tribromophenyl*)-3 : 4-*dihydrophthalazine*-4-*acetic acid* (IV), and the 3′- and 4′-*chlorophenyl* analogues were prepared similarly. All were converted by aqueous sulphuric acid (b. p. 140°) into the corresponding *halogeno*-3-*phenylphthalaz*-1-*ones*, or by cold acid dichromate into the respective *halogeno*-3-*phenyl*-4-*methylphthalaz*-1-*ones*. 1-*Methoxy*-3-(2′ : 4′ : 6′-*tribromophenyl*)-4-*methylene*-3 : 4-*dihydrophthalazine* and chloro-2 : 4-dinitrobenzene or 1-phenyl-3-methyl-4-anilinomethylene-5-pyrazolone afforded 1-*methoxy*-3-(2′ : 4′ : 6′-*tribromophenyl*)-4-(2″ : 4″-*dinitrobenzylidene*)- or -4-(5″-*keto*-1″-*phenyl*-3″-*methylpyrazolinylidene-ethylidene*)-3 : 4-*dihydrophthalazine*, respectively.

In general, the reactions of (IV) and its analogues follow the expected courses, and are recorded in the experimental section. Several anomalies, however, occur. Thus, Clemmensen reduction of 3′- and 4′-*chloro*-3-*phenylphthalaz*-1-*one* afforded 3′- and 4′-*chloro*-N-*phenylphthalimidine* respectively, but, in a similar reaction, 2′ : 4′ : 6′-*tribromo*-3-*phenylphthalaz*-1-*one* lost a bromine atom to yield 2′ : 4′-*dibromo*-N-*phenylphthalimidine*. Fission occurred during the Clemmensen

* The nomenclature in this paper follows that of earlier papers of the series.

reduction of 2′ : 4′ : 6-*tribromo*-3-*phenyl*-4-*methylphthalaz*-1-*one*, with formation of 2 : 4: 6-tribromoaniline; 3′-*chloro*-3-*phenyl*-4-*methylphthalaz*-1-*one* (V), however, yielded 1-*keto*-3-(3′-*chlorophenyl*)-4-*methyltetrahydrophthalazine* (VI), whilst a similar reduction of the 4′-*chloro*-analogue (VII) of (V) gave 4′-*chloro*-N-*phenyl*-3-*methylphthalimidine* (VIII).



With aqueous potassium permanganate at 70°, (IV) afforded 1 : 4-*diketo*-3-(2′ : 4′ : 6′-*tribromophenyl*)*tetrahydrophthalazine* (IX); the retention of all the bromine in this vigorous reaction is noteworthy, in view of the fact that bromine is lost during a similar reaction with the 2 : 6-dibromo-4-nitro-analogue (cf. *J.*, 1935, 1808).

Compound (IX) could not be methylated through its silver salt, but 1-*methoxy*-4-*keto*-3-(2′ : 4′ : 6′-*tribromophenyl*)-3 : 4-*dihydrophthalazine* was conveniently prepared by refluxing 1-methoxy-3-(2′ : 4′ : 6′-tribromophenyl)-4-methylene-3 : 4-dihydrophthalazine with *p*-nitrosodimethylaniline in alcohol.

Rowe, Adams, and Peters (*J.*, 1937, 9) noted the retarding influence of halogen on the conversion of nitroaryl-3-phenylphalaz-1-ones and their 1-methyl homologues into the isomeric 4-ones. When 2′ : 4′ : 6′-tribromo- and 3′-chloro-3-phenylphthalaz-1-one and their 4-methyl-derivatives were heated with aqueous hydrochloric acid (1 : 8) in a sealed tube at 190—200° for 6 hours, only unchanged material was recovered; prolonged reaction, *e.g.*, for 60 hours, caused considerable isomerisation with the 3′-chloro-derivatives, but only slight with the 2′ : 4′ : 6′-tribromo-compounds. The derived products were shown to be identical with synthetic specimens of 2′ : 4′ : 6′-*tribromo*- and 3′-*chloro*-3-*phenylphthalaz*-4-*one* and their 1-*methyl* derivatives respectively.

Experimental.

Sodium Hydrogen 3-(2′ : 4′ : 6′-*tribromophenyl*)-3 : 4-*dihydrophthalazine*-1-*sulphonate*-4-*acetate* (III).—A filtered solution of commercial 50% sodium β-naphthol-1-sulphonate (50 g.) in water (250 c.c.) was stirred at 0° into a solution of diazotised 2 : 4 : 6-tribromoaniline, prepared by dissolving dry sodium nitrite (9 g.) in concentrated sulphuric acid (150 c.c.) at 50° and adding the base (33 g.) to it, followed by pouring the mixture on ice (400 g.), with stirring. The straw-coloured precipitate of 2′ : 4′ : 6′-tribromobenzene-2-naphthol-1-diazosulphonate was washed free from acid with brine, mixed with cold water (200 c.c.), and powdered sodium carbonate added. After addition of 30 g., the resulting suspension of sodium 1-(2′ : 4′ : 6′-tribromobenzeneazo)-β-naphthaquinone-1-sulphonate was added to a solution of sodium hydroxide (60 g.) in ice-cold water, and the mixture left overnight. It was then acidified with concentrated hydrochloric acid and made alkaline with sodium carbonate solution. After removal of the 2′ : 4′ : 6′-tribromobenzeneazo-β-naphthol (4·5 g.; 8·6%) by filtration, it was acidified again and the *sodium hydrogen* salt was collected; it crystallised from water in minute colourless prisms (50 g.; 82%). It lost water of crystallisation at 120° (Found: loss at 120°, 10·4. $C_{16}H_{10}O_5N_2Br_3SNa,4H_2O$ requires H_2O, 10·6%. Found in dried material: S, 5·2; Br, 39·2. $C_{16}H_{10}O_5N_2Br_3SNa$ requires S, 5·3; Br, 39·6%).

1-*Hydroxy*-3-(2′ : 4′ : 6′-*tribromophenyl*)-3 : 4-*dihydrophthalazine*-4-*acetic Acid* (IV).—A solution of the preceding sodium hydrogen salt (20 g.) in water (400 c.c.) was boiled, and concentrated hydrochloric acid (65 c.c.) added gradually until evolution of sulphur dioxide ceased and the *acid* (IV) separated in a granular condition (12 hours). It was washed with warm water and dried; it then crystallised from acetic acid in colourless prisms, m. p. 227—228° (12 g.; 66·6%) (Found: C, 36·9; H, 2·5; N, 5·3; Br, 46·1. $C_{16}H_{11}O_3N_2Br_3$ requires C, 37·0; H, 2·1; N, 5·4; Br, 46·2%). The *methyl* ester crystallised from methyl alcohol in colourless prisms, m. p. 172° (Found: C, 38·2; H, 2·6; N, 5·4. $C_{17}H_{13}O_3N_2Br_3$ requires C, 38·3; H, 2·4; N, 5·25%). The *N*-methyl ether, 1-*keto*-3-(2′ : 4′ : 6′-*tribromophenyl*)-2-*methyltetrahydrophthalazine*-4-*acetic acid*, crystallised from alcohol in small colourless prisms, m. p. 239—240° (Found: C, 38·5; H, 2·7; N, 4·95. $C_{17}H_{13}O_3N_2Br_3$ requires C, 38·3; H, 2·4; N, 5·25%). The *anilide* crystallised from acetic acid in colourless prisms, m. p. 266° (Found: loss at 135°, 16·6. $C_{22}H_{16}O_2N_3Br_3,2C_2H_4O_2$ requires $C_2H_4O_2$, 16·8%. Found in material heated at 135°; C, 44·2; H, 2·6; N, 7·0; Br, 39·9. $C_{22}H_{16}O_2N_3Br_3$ requires C, 44·4; H, 2·7; N, 7·1; Br, 40·4%). 1-*Acetoxy*-3-(2′ : 4′ : 6′-*tribromophenyl*)-3 : 4-*dihydrophthalazine*-4-*acetic acid* crystallised from acetic acid in colourless prisms, m. p. 231—232° (decomp.) (Found: C, 38·6; H, 2·5; N, 4·6. $C_{18}H_{13}O_4N_2Br_3$ requires C, 38·5; H, 2·3; N, 5·0%).

2′ : 4′ : 6′-*Tribromo*-3-*phenylphthalaz*-1-*one*.—(*a*) A solution of 1-hydroxy-3-(2′ : 4′ : 6′-tribromophenyl)-3 : 4-dihydrophthalazine-4-acetic acid (3·4 g.) in concentrated sulphuric acid (17 c.c.) and water (20 c.c.) was refluxed for 1·5 hours; the solution was diluted with water (30 c.c.) and filtered (charcoal); colourless needles of the sulphate then separated; these were collected and basified with sodium carbonate. The *phthalazone* crystallised from alcohol in colourless prismatic needles, m. p. 305° (decomp.) (2 g.; 66·6%) (Found: C, 37·0; H, 1·6; N, 6·1; Br, 52·5. $C_{16}H_7ON_2Br_3$ requires C, 36·6; H, 1·5; N, 6·1; Br, 52·3%), which turned blue on exposure to light. The *picrate* separated from

alcohol in bright yellow rectangular prisms, m. p. 266° (decomp.) (Found : C, 35·1; H, 1·8; Br, 34·3. $C_{20}H_{10}O_6N_2Br_2$ requires C, 34·9; H, 1·45; Br, 34·8%).

(*b*) 1-Hydroxy-3-(2′ : 4′ : 6′-tribromophenyl)-3 : 4-dihydrophthalazine-4-acetic acid (10 g.) was dissolved in concentrated sulphuric acid (50 c.c.), acetic acid (60 c.c.) added, and the solution refluxed gently for 15 minutes. On pouring on ice, the sulphate separated and was converted into the phthalazone (5·5 g.; 62·5%).

Action of Methyl Sulphate.—2′ : 4′ : 6′-Tribromo-3-phenylphthalaz-1-one (6 g.) was dissolved in nitrobenzene (120 c.c.), and the temperature gradually raised to 125°. Methyl sulphate (3 g.) was added, and, after 45 minutes at the same temperature, nitrobenzene was removed with steam and the aqueous residue was made alkaline with sodium carbonate. The almost colourless precipitate was washed with water and dried (5 g.). It crystallised from ethyl alcohol in small, almost colourless prisms, m. p. 135—136° (Found : C, 39·3; H, 2·9; N, 5·1; Br, 46·5. $C_{17}H_{10}O_2N_2Br_3$ requires C, 39·3; H, 2·9; N, 5·4; Br, 46·2%), or from methyl alcohol in larger, pale yellow prismatic needles, m. p. 138—139° (Found : C, 38·2; H, 2·6; N, 5·5. $C_{16}H_{12}O_2N_2Br_2$ requires C, 38·0; H, 2·6; N, 5·5%).

2′ : 4′-*Dibromo*-N-*phenylphthalimidine.*—A solution of the above phthalazone (2 g.) in water (20 c.c.), hydrochloric acid (50 c.c.), alcohol (20 c.c.), and acetic acid (20 c.c.) was heated with zinc amalgam (70 g.) at 90° for 5 hours. The mixture was cooled, filtered, and poured on ice; the *phthalimidine* crystallised from alcohol in colourless prisms, m. p. 126—127° (0·7 g.; 43·7%) (Found : C, 46·2; H, 2·4; N, 4·0; Br, 43·1. $C_{14}H_9ONBr_2$ requires C, 45·9; H, 2·2; N, 3·8; Br, 43·7%).

1 : 4-*Diketo*-3-(2′ : 4′ : 6′-*tribromophenyl*)*tetrahydrophthalazine* (IX).—Finely powdered potassium permanganate (15 g.) was added during 5 minutes to a suspension of 1-hydroxy-3-(2′ : 4′ : 6′-tribromophenyl)-3 : 4-dihydrophthalazine-4 -acetic acid (10 g.) in water (150 c.c.) at 70°. Reaction was vigorous, and the mixture was boiled and filtered hot; the yellow filtrate was cooled and acidified with hydrochloric acid. The *tetrahydrophthalazine* crystallised from acetic acid in small, colourless prismatic needles, m. p. 333—334° (6 g.; 63·2%) (Found : C, 35·7; H, 1·5; N, 5·6. $C_{14}H_7O_2N_2Br_3$ requires C, 35·4; H, 1·5; N, 5·9%). The *silver* salt (Found : Ag, 18·5. $C_{14}H_6O_2N_2Br_3Ag$ requires Ag, 18·5%) did not react with methyl iodide in dry benzene.

2′ : 4′ : 6′-*Tribromo*-3-*phenyl*-4-*methylphthalaz*-1-*one.*—(*a*) 1-Hydroxy-3-(2′ : 4′ : 6′-tribromophenyl)-3 : 4-dihydrophthalazine-4-acetic acid (10 g.) was dissolved in cold concentrated sulphuric acid (75 c.c.), and the solution poured on ice (250 g.). Finely powdered potassium dichromate (3 g.) was added, with stirring, during 2 hours, and the yellow precipitate of the sulphate of the phthalazone was collected and basified with warm aqueous ammonia. The *phthalazone* crystallised from alcohol in pale greenish prisms, melting at 150°, solidifying and remelting at 252° (6·6 g.; 72·5%) (Found : loss at 120°, 4·3. $C_{15}H_9ON_2Br_3,0{\cdot}5C_2H_6O$ requires C_2H_6O, 4·6%. Found in material heated at 120° : C, 37·9; H, 2·0; N, 5·6; Br, 50·4. $C_{15}H_9ON_2Br_3$ requires C, 38·0; H, 1·9; N, 5·9; Br, 50·7%). Its *picrate* crystallised from dry alcohol in yellow rhombs, m. p. 249° (Found : N, 10·1; Br, 34·1. $C_{21}H_{12}O_8N_5Br_3$ requires N, 10·0; Br, 34·1%).

(*b*) 1-Hydroxy-3-(2′ : 4′ : 6′-tribromophenyl)-3 : 4-dihydrophthalazine-4-acetic acid (2 g.) was dissolved in nitric acid (*d* 1·51; 20 c.c.), and the solution heated at 50° for 4 minutes, poured on ice, and the precipitated nitrate collected and basified with warm aqueous ammonia. The product crystallised from ethyl acetate in colourless prisms, m. p. 252°, of 3-(2′ : 4′ : 6′-tribromophenyl)-4-methylphthalaz-1-one (1·1 g.; 48·8%).

1-*Methoxy*-3-(2′ : 4′ : 6′-*tribromophenyl*)-4-*methylene*-3 : 4-*dihydrophthalazine.*—2′ : 4′ : 6′-Tribromo-3-phenyl-4-methylphthalaz-1-one (5·6 g.) was dissolved in dry nitrobenzene (40 c.c.) at 130°, and methyl sulphate (4 c.c.) added. The solution was left for 1 hour at the same temperature, nitrobenzene removed with steam, the aqueous residue filtered from a little resin, and the filtrate made alkaline with sodium carbonate solution. The *methylene base* crystallised from alcohols, but better from ethyl acetate, in pale yellow, prismatic needles, m. p. 153° (3 g.; 63·3%) (Found : C, 39·1; H, 2·7; N, 5·9; Br, 48·7. $C_{16}H_{11}ON_2Br_3$ requires C, 39·4; H, 2·3; N, 5·75; Br, 49·2%), readily soluble in dilute mineral acids to give colourless solutions. Addition of 60% perchloric acid (10 c.c.) to the methylene derivative (1 g.) in hydrochloric acid (5 c.c.) and water (30 c.c.) gave the *perchlorate*, which crystallised from alcohol containing a trace of perchloric acid, in colourless prisms, m. p. 230° (Found : C, 33·05; H, 2·0; 4·755 mg. gave 5·68 mg. AgCl + AgBr. $C_{16}H_{11}O_6N_2ClBr_3$ requires C, 32·7; H, 1·7%; AgCl + AgBr, 5·735 mg.), decomposed by aqueous alkalis to give the base.

1-*Methoxy*-3-(2′ : 4′ : 6′-*tribromophenyl*)-4-(5″-*keto*-1″-*phenyl*-3″-*methylpyrazolinylidene*-*ethylidene*)-3 : 4-*dihydrophthalazine.*—A solution of 1-methoxy-3-(2′ : 4′ : 6′-tribromophenyl)-4-methylene-3 : 4-dihydrophthalazine (1 g.) and 1-phenyl-3-methyl-4-anilinomethylene-5-pyrazolone (1 g.) in acetic anhydride (5 c.c.) and acetic acid (6 c.c.) was heated at 100° for 9 hours. The *compound* crystallised from acetic anhydride in greenish-black prisms, m. p. 224° (0·6 g.; 44%) (Found : N, 8·3. $C_{27}H_{19}O_2N_4Br_3$ requires N, 8·3%).

1-*Methoxy*-3-(2′ : 4′ : 6′-*tribromophenyl*)-4-(2″ : 4″-*dinitrobenzylidene*)-3 : 4-*dihydrophthalazine.*—2 : 4-Dinitrochlorobenzene (1·2 g.) was added to a suspension of 1-methoxy-3-(2′ : 4′ : 6′-tribromophenyl)-4-methylene-3 : 4-dihydrophthalazine (2 g.) in hot alcohol (60 c.c.), and the mixture refluxed for 4 hours. A deep red colour developed rapidly, and concentration to 50 c.c., followed by cooling at 0°, gave a tar which slowly solidified; the *compound* was crystallised several times from alcohol; it separated in dark red needles, m. p. 138—140° (0·6 g.; 23%) (Found : C, 40·6; H, 2·1; N, 8·1. $C_{23}H_{13}O_8N_4Br_3$ requires C, 40·4; H, 2·0; N, 8·5%), soluble in concentrated sulphuric acid with a yellow colour.

o-*Carboxybenzaldehyde* 2′ : 4′ : 6′-*Tribromophenylhydrazone.*—2 : 4 : 6-Tribromophenylhydrazine (3·7 g.) was dissolved in cold benzene (400 c.c.) and the solution added to a solution of *o*-phthalaldehydic acid (1·5 g.) in cold benzene (400 c.c.). After 2 hours, the *carboxy*-derivative had separated in colourless needles, m. p. 204° (2·7 g.; 51·7%) (Found : C, 35·5; H, 1·9; N, 6·0; Br, 50·8. $C_{14}H_9O_2N_2Br_3$ requires C, 35·2; H, 5·8; N, 5·8; Br, 50·3%).

2′ : 4′ : 6′-*Tribromo*-3-*phenylphthalaz*-4-*one.*—*o*-Carboxybenzaldehyde 2′ : 4′ : 6′-tribromophenylhydrazone (2 g.) was dissolved in amyl alcohol (20 c.c.), and the solution saturated with dry hydrogen

chloride. The solution was then refluxed for 1 hour, and the *phthalazone* collected; it crystallised from acetic acid in small colourless prisms, m. p. 182° (0·8 g.; 40·8%) (Found: C, 36·9; H, 1·6; N, 5·8; Br, 52·3. $C_{14}H_7ON_2Br_3$ requires C, 36·7; H, 1·5; N, 6·1; Br, 52·3%), insoluble in mineral acids and aqueous alkalis. It was obtained also by heating 3-(2′ : 4′ : 6′-tribromophenyl)phthalaz-1-one (1·4 g.) with aqueous hydrochloric acid (1 : 8; 18 c.c.) at 190—200° for 64 hours (0·1 g.; 7%).

o-Carboxyacetophenone 2′ : 4′ : 6′-Tribromophenylhydrazone.—A solution of acetophenone-*o*-carboxylic acid (2 g.) in boiling alcohol (10 c.c.) was added to a solution of 2 : 4 : 6-tribromophenylhydrazine (3 g.) in alcohol (80 c.c.). On standing, the *hydrazone* separated progressively in almost colourless needles, needles, m. p. 171° (3 g.; 71·4%) (Found: C, 37·15; H, 2·4; N, 5·7; Br, 49·3. $C_{15}H_{11}O_2N_2Br_3$ requires C, 36·6; H, 2·2; N, 5·7; Br, 48·8%), soluble in cold aqueous alkalis.

2′ : 4′ : 6′-Tribromo-3-phenyl-1-methylphthalaz-4-one.—*o*-Carboxyacetophenone 2′ : 4′ : 6′-tribromophenylhydrazone (2 g.) was refluxed with acetic acid (40 c.c.) for 3 hours; on cooling, the *phthalazone* separated in colourless needles, m. p. 195° (1·2 g.; 61·2%) (Found: C, 37·7; H, 2·2; N, 5·6. $C_{15}H_9ON_2Br_3$ requires C, 38·0; H, 1·9; N, 5·9%), insoluble in mineral acids and alkalis. It was also obtained in low yield by heating the isomeric 4-methylphthalaz-1-one with aqueous hydrochloric acid (1 : 8) in a sealed tube at 190—200° for 52 hours.

Sodium Hydrogen 3-(3′-Chlorophenyl)-3 : 4-dihydrophthalazine-1-sulphonate-4-acetate.—The *salt* was prepared in an analogous manner to that given for the 2′ : 4′ : 6′-tribromo-derivative; it was precipitated by ether from a solution in ethyl acetate as a yellow solid (55% yield) (Found: S, 6·6. $C_{16}H_{12}O_5N_2SClNa$ requires S, 7·9%).

1-Hydroxy-3-(3′-chlorophenyl)-3 : 4-dihydrophthalazine-4-acetic Acid.—This was obtained in 26% yield by hydrolysis of the above sodium salt; it crystallised from acetic acid in colourless prisms, m. p. 200° (Found: C, 60·6; H, 3·9; N, 8·9; Cl, 11·3. $C_{16}H_{13}O_3N_2Cl$ requires C, 60·75; H, 4·1; N, 8·9; Cl, 11·0%). The *methyl* ester crystallised from methyl alcohol in minute, colourless prisms, m. p. 123° (Found: C, 61·9; H, 4·6; N, 8·6. $C_{17}H_{15}O_3N_2Cl$ requires C, 61·7; H, 4·55; N, 8·5%). The *N-methyl ether* crystallised from alcohol in colourless prisms, m. p. 197° (Found: N, 8·55; Cl, 10·7. $C_{17}H_{15}O_3N_2Cl$ requires N, 8·5; Cl, 10·7%). The *anilide* crystallised from toluene in clusters of small yellow needles, m. p. 173—175° (Found: N, 10·5; Cl, 9·0. $C_{22}H_{18}O_2N_3Cl$ requires N, 10·7; Cl, 9·0%). *1-Acetoxy-3-(3′-chlorophenyl)-3 : 4-dihydrophthalazine-4-acetic acid* crystallised from acetic acid in colourless prisms, m. p. 175—176° (Found: N, 8·0; Cl, 9·7. $C_{18}H_{15}O_4N_2Cl$ requires N, 7·8; Cl, 9·9%), soluble in cold aqueous sodium carbonate with a yellow colour.

3′-Chloro-3-phenylphthalaz-1-one.—1-Hydroxy-3-(3′-chlorophenyl)-3 : 4-dihydrophthalazine-4-acetic acid (4 g.) was refluxed with concentrated sulphuric acid (30 c.c.) and water (35 c.c.) for 3 hours. The *phthalazone*, isolated in the usual manner, crystallised from alcohol in colourless prisms, m. p. 278° (2·5 g.; 78·1%) (Found: C, 65·0; H, 3·7; N, 10·7; Cl, 14·1. $C_{14}H_9ON_2Cl$ requires C, 65·5; H, 3·5; N, 10·9; Cl, 13·8%). It gave a *picrate*, minute yellow plates, m. p. 253—254° (Found: N, 14·1. $C_{20}H_{12}O_8N_5Cl$ requires N, 14·4%).

3′-Chloro-N-phenylphthalimidine.—3′-Chloro-3-phenylphthalaz-1-one (1 g.) was dissolved in hydrochloric acid (20 c.c.), water (10 c.c.), alcohol (10 c.c.), and acetic acid (20 c.c.), and the solution was warmed with zinc amalgam (30 g.) at 75° for 2 hours. The *phthalimidine* crystallised from alcohol in colourless needles, m. p. 185° (0·4 g.; 84%) (Found: C, 69·3; H, 4·0; N, 6·0; Cl, 14·6. $C_{14}H_{10}ONCl$ requires C, 68·9; H, 4·0; N, 5·75; Cl, 14·9%).

3′-Chloro-3-phenyl-4-methylphthalaz-1-one Sulphate.—1-Hydroxy-3-(3′-chlorophenyl)-3 : 4-dihydrophthalazine-4-acetic acid (15 g.) was dissolved in concentrated sulphuric acid (120 c.c.) and poured on ice (300 g.). Finely powdered potassium dichromate (8 g.) was added gradually with cooling. The green solution was stirred for 3 hours at room temperature and then neutralised with aqueous sodium hydroxide. Extraction of the precipitate with aqueous alcohol gave a solid which crystallised with difficulty from the same solvent in colourless cubes, m. p. 320°, of the *sulphate* (9·5 g.; 64·6%) (Found: C, 47·9; H, 3·8; Cl, 9·5. $C_{15}H_{13}O_5N_2ClS$ requires C, 48·8; H, 3·5; Cl, 9·5%). Basification with ammonia or sodium carbonate or hydroxide gave only an intractable tar, which yielded a *picrate*, yellow needles, m. p. 219° (Found: N, 13·8. $C_{21}H_{14}O_9N_5Cl$ requires N, 14·0%).

1-Keto-3-(3′-chlorophenyl)-4-methyltetrahydrophthalazine (VI).—3′-Chloro-3-phenyl-4-methylphthalaz-1-one sulphate (1 g.) was warmed with hydrochloric acid (20 c.c.), water (20 c.c.), alcohol (10 c.c.), and acetic acid (7 c.c.). The temperature was raised to 90°, and zinc amalgam (60 g.) added, and after 3 hours at the same temperature the mixture was poured on ice; the precipitate of *tetrahydrophthalazine* crystallised from alcohol in colourless rhombs, m. p. 178° (0·5 g.; 50%) (Found: C, 66·1; H, 4·6; Cl, 12·6. $C_{15}H_{13}ON_2Cl$ requires C, 66·05; H, 4·8; Cl, 13·0%).

1 : 4-Diketo-3-(3′-chlorophenyl)tetrahydrophthalazine.—A suspension of 1-hydroxy-3-(3′-chlorophenyl)-3 : 4-dihydrophthalazine-4-acetic acid (5 g.) in water (100 c.c.) was treated with potassium permanganate (8 g.) at 70° during 5 minutes. The reaction was vigorous, and, after it had subsided, the mixture was boiled for 5 minutes and filtered, and the filtrate was acidified; the *tetrahydrophthalazine* crystallised from aqueous alcohol in almost colourless prisms, m. p. 226—230° (0·85 g.; 19·7%) (Found: C, 60·9; H, 3·7; N, 10·1. $C_{14}H_9O_2N_2Cl$ requires C, 61·2; H, 3·3; N, 10·2%), soluble in cold aqueous ammonia with a yellow colour.

3′-Chloro-3-phenylphthalaz-4-one.—A solution of *m*-chlorophenylhydrazine (2 g.) in alcohol (8 c.c.) was refluxed with a solution of *o*-phthalaldehydic acid (2 g.) in alcohol (12 c.c.) for 1 hour. The *phthalazone* crystallised from alcohol in colourless needles, m. p. 135° (yield, 1·5 g.; 41·6%) (Found: C, 65·8; H, 3·5; N, 10·9; Cl, 13·95. $C_{14}H_9ON_2Cl$ requires C, 65·5; H, 3·5; N, 10·9; Cl, 13·8%). It is insoluble in mineral acids and alkalis and does not form a picrate. It was also obtained in 71% yield by heating the isomeric phthalaz-1-one with aqueous hydrochloric acid (1 : 8) at 200° in a sealed tube for 60 hours.

3′-Chloro-3-phenyl-1-methylphthalaz-4-one.—Alcoholic solutions of *m*-chlorophenylhydrazine (1·4 g. in 10 c.c.) and acetophenone-*o*-carboxylic acid (1·4 g. in 10 c.c.) were mixed cold and then refluxed for 20 minutes. The *compound* separated in clusters of colourless needles, m. p. 140° (1·3 g.; 50%) (Found: C, 66·6; H, 4·1; N, 10·2. $C_{15}H_{11}ON_2Cl$ requires C, 66·5; H, 4·0; N, 10·3%), insoluble in acids or

alkalis. A 60% conversion of the isomeric 4-methyl-1-one into the 1-methyl-4-one was effected by aqueous hydrochloric acid (1 : 8) at 200° in a sealed tube for 55 hours.

Sodium Hydrogen 3-(4′-*Chlorophenyl*)-3 : 4-*dihydrophthalazine*-1-*sulphonate*-4-*acetate*.—This was isolated in the usual manner, but was resinous (Found : N, 5·3. $C_{16}H_{13}O_5N_2SClNa$ requires N, 6·9%).

1-*Hydroxy*-3-(4′-*chlorophenyl*)-3 : 4-*dihydrophthalazine*-4-*acetic Acid*.—Hydrolysis of the above salt yielded the *hydroxy*-compound, which crystallised from acetic acid in colourless needles, m. p. 236° (Found : N, 9·2; Cl, 10·8. $C_{16}H_{13}O_3N_2Cl$ requires N, 8·9; Cl, 11·0%).

4′-*Chloro*-3-*phenylphthalaz*-1-*one*.—A solution of the above hydroxy- compound (10 g.) in concentrated sulphuric acid (70 c.c.) and water (84 c.c.) was refluxed for 2 hours. The *phthalaz*-1-*one* separated from alcohol in colourless needles, m. p. 281—283° (3·6 g.; 44·4%) (Found : C, 65·3; H, 3·7; N, 10·6; Cl, 14·2. $C_{14}H_9ON_2Cl$ requires C, 65·5; H, 3·5; N, 10·9; Cl, 13·8%).

4′-*Chloro*-N-*phenylphthalimidine*.—Prepared as for the 3′-chloro-analogue, this *compound* crystallised from alcohol in colourless, hexagonal plates, m. p. 180° (Found : C, 68·9; H, 4·0. $C_{14}H_{10}ONCl$ requires C, 68·9; H, 4·0%).

4′-*Chloro*-3-*phenyl*-4-*methylphthalaz*-1-*one* (VII).—This crystallised from alcohol in colourless, prismatic needles, shrinking at 220° and melting at 238°, turning green in air; the *picrate* separated from dry alcohol in yellow rectangular prisms, m. p. 200° (Found : N, 14·1. $C_{21}H_{14}O_8N_5Cl$ requires N, 14·0%).

4′-*Chloro*-N-*phenyl*-3-*methylphthalimidine* (VIII).—4′-Chloro-3-phenyl-4-methylphthalaz-1-one (1 g.) was refluxed with zinc amalgam (35 g.) in hydrochloric acid (20 c.c.), alcohol (10 c.c.), acetic acid (10 c.c.) and water (10 c.c.) for 3 hours. The *phthalimidine* crystallised from alcohol in colourless prismatic needles, m. p. 185° (0·5 g.; 71%) (Found : C, 70·2; H, 4·3. $C_{15}H_{12}ONCl$ requires C, 69·9; H, 4·6%).

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124. *The Synthesis of Some* p-*Arylsulphonylbenzaldehydes and Related Aldehydes and Ketones.*

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Representative *p*-arylsulphonylbenzaldehydes were obtained by the route, $Ar{\cdot}SO_2{\cdot}C_6H_4Me \longrightarrow Ar{\cdot}SO_2{\cdot}C_6H_4{\cdot}CH(OAc)_2 \longrightarrow Ar{\cdot}SO_2{\cdot}C_6H_4{\cdot}CHO$, provided that the group Ar was not susceptible to oxidation by chromic oxide. Related aldehydes and ketones were prepared by standard methods. Phenyl thiolacetate, PhSAc, did not undergo the Fries rearrangement or the Friedel–Crafts reaction, but the latter method was successful with thioanisole.

IN connection with an investigation which we are carrying out on the synthesis of various diaryl sulphones of possible chemotherapeutic interest, we required various *p*-arylsulphonylbenzaldehydes as intermediates. An obvious route was by way of the *p*-arylsulphonylbenzonitriles, since Fuller, Tonkin, and Walker (*J.*, 1945, 633) have shown that *p*-methylsulphonylbenzaldehyde was readily obtained from *p*-methylsulphonylbenzonitrile by Stephen's method (*J.*, 1925, **127**, 1874). The preparation of *p*-arylsulphonylbenzonitriles was not readily accomplished by the methods we investigated. Thus, attempted condensation of various aryl iodides with sodium *p*-cyanobenzenesulphinate was not successful. A possible alternative route, as exemplified by the reaction between resorcinol dimethyl ether and *p*-cyanobenzenesulphonyl chloride in the presence of zinc chloride (Burton and Hoggarth, *J.*, 1945, 14), was studied, but the product was not homogeneous.

Since many *p*-tolyl aryl sulphones can be prepared simply and, according to the nature of the aryl group, in fairly good yield, we decided to investigate an alternative method, namely, the oxidation by chromic oxide in an acetic acid–acetic anhydride–sulphuric acid medium. This procedure is known (Liebermann and Connor, *Org. Synth.*, Coll. Vol., II, 1943, 441) to work well for substituted toluenes provided that these do not contain a group susceptible to oxidation. Application of this method to phenyl, p-*chlorophenyl*, p-*methoxyphenyl*, and 3 : 4-*dimethoxyphenyl* p-*tolyl sulphones* has given the corresponding p-*phenyl*-, 4-p-*chlorophenyl*-, and 4-p-*methoxyphenyl*-*benzaldehydes* in yields of 60, 71, and 10%, respectively, but no 4-3′ : 4′-dimethoxyphenylbenzaldehyde. This aldehyde was not obtained nor was the yield of anisyl analogue improved by using chromyl chloride as the oxidising agent. The results with the methoxyl compounds were not unexpected, since the methoxylated aryl group must be more susceptible to oxidative rupture than either phenyl or *p*-chlorophenyl. *p*-Phenylsulphonylbenzaldehyde was also obtained from *p*-phenylsulphonyl-benzonitrile or -benzanilide by direct reduction or reduction of the corresponding imino-chloride by ethereal stannous chloride–hydrogen chloride.

A moderate yield of p-*sulphamylbenzaldehyde* can also be obtained by the above chromic oxide oxidation of *p*-toluenesulphonamide; a better procedure was to apply Stephen's method to *p*-cyanobenzenesulphonamide.

This investigation was in progress at the time of publication of the paper by Fuller, Tonkin,

and Walker (*loc. cit.*), and we had prepared certain of the intermediates described therein. Although these authors failed to prepare *p*-methylsulphonylacetophenone by the Grignard method we had obtained a 17% yield using methylmagnesium iodide and *p*-methylsulphonylbenzonitrile in an ether–benzene medium. It is true that the reaction did not proceed smoothly, but the nature of the Grignard reagent as well as the methylsulphonyl group was apparently of some importance, since phenylmagnesium bromide with the same nitrile gave a good yield of p-*methylsulphonylbenzophenone*. As expected, we had no difficulty in preparing p-*phenylsulphonylacetophenone* from *p*-phenylsulphonylbenzonitrile and methylmagnesium iodide.

For the preparation of *p*-alkylthioacetophenones we first explored the possibility of obtaining the parent thiol by the Friedel–Crafts reaction or the Fries rearrangement using phenyl thiolacetate, PhSAc. No ketone was obtained by either method under a variety of experimental conditions. The Friedel–Crafts reaction was, however, successfully carried out on thioanisole, and proof that the product was p-*methylthioacetophenone* was obtained by oxidation of this to *p*-methylsulphonylacetophenone.

Experimental.

Phenyl *p*-tolyl sulphone was obtained in 90% yield by Newell's procedure (*Amer. Chem. J.*, 1898, **20**, 303).

p-*Chlorophenyl* p-*Tolyl Sulphone* (4-*Chloro*-4′-*methyldiphenyl Sulphone*).—Powdered aluminium chloride (30 g.) was added in small portions to a solution of *p*-toluenesulphonyl chloride (40 g.) in chlorobenzene (55 g.) kept at 90°. The mixture was then heated at 95° for 1 hour and the cooled product added to warm dilute hydrochloric acid. Excess of chlorobenzene was removed by steam distillation. The *sulphone* (45 g.) crystallised from alcohol in colourless prisms, m. p. 124° (Found: C, 58·4; H, 4·5. $C_{13}H_{11}O_2ClS$ requires C, 58·5; H, 4·1%).

p-*Methoxyphenyl* p-*Tolyl Sulphone* (4-*Methoxy*-4′-*methyldiphenyl Sulphone*).—Aluminium chloride (30 g.) was added in small portions to a solution of *p*-toluenesulphonyl chloride (40 g.) in anisole (40 g.) at 75°. Further heating at 80—90° for 1 hour, followed by decomposition with dilute hydrochloric acid and steam distillation, gave the crude sulphone which was shaken vigorously with hot 2N-sodium hydroxide (100 c.c.). Acidification of the alkaline filtrate gave a small amount of a phenolic substance, presumably 4-hydroxy-4′-methyldiphenyl sulphone, m. p. 125°. The insoluble 4-*methoxy*-4′-*methyldiphenyl sulphone* (40 g.) recrystallised from alcohol in colourless needles, m. p. 104—105° (Found: C, 64·1; H, 5·5. $C_{14}H_{14}O_3S$ requires C, 64·1; H, 5·3%).

3 : 4-*Dimethoxyphenyl* p-*Tolyl Sulphone* (3 : 4-*Dimethoxy*-4′-*methyldiphenyl Sulphone*).—Aluminium chloride (30 g.) was added in small portions, with frequent shaking, to *p*-toluenesulphonyl chloride (40 g.) in veratrole (50 c.c.) at 100°. After ½ hour at 130° (bath temp.), the resulting dark green viscous liquid was decomposed and purified as for the *p*-methoxyphenyl analogue. The *sulphone* (25 g.) separated from 95% alcohol in colourless needles, m. p. 128° (Found: C, 61·7; H, 5·6. $C_{15}H_{16}O_4S$ requires C, 61·6; H, 5·4%).

p-*Phenylsulphonylbenzaldehyde*.—(*a*) To a cold, well-stirred solution of phenyl *p*-tolyl sulphone (16 g.) in a mixture of glacial acetic acid (150 c.c.), acetic anhydride (115 c.c.), and concentrated sulphuric acid (17 c.c.), small amounts of chromic oxide (20 g.) were added so that the temperature was kept below 10°. Stirring was then continued in the cold until all the oxide had dissolved (4—5 hours). The crude *diacetate*, obtained when the mixture was poured into ice-water (1000 c.c.), had m. p. 153—154° after crystallisation from alcohol (Found: C, 58·4; H, 4·8; S, 9·7. $C_{17}H_{16}O_6S$ requires C, 58·5; H, 4·6; S, 9·2%), and was hydrolysed without further purification by boiling for 1½ hours with alcohol (50 c.c.), water (30 c.c.), and concentrated sulphuric acid (2 c.c.). The hot hydrolysis mixture was filtered from a little insoluble matter and cooled. The *aldehyde* (10 g.) which separated crystallised from benzene in colourless needles, m. p. 128°, raised to 130° by further crystallisation from 50% alcohol (Found: C, 63·5; H, 4·2. $C_{13}H_{10}O_3S$ requires C, 63·4; H, 4·1%). The aldehyde formed a solid sodium hydrogen sulphite compound which could be used conveniently for purification.

(*b*) A solution of *p*-phenylsulphonylbenzonitrile (24 g.) (Fuller, Tonkin, and Walker, *loc. cit.*) in chloroform (160 c.c.) was added to a Stephen's reagent prepared from anhydrous stannous chloride (36 g.), and the mixture shaken for 7 hours. After being kept overnight the solid stannichloride was decomposed by water, and the aldehyde (20 g.) isolated from a chloroform solution through its sodium hydrogen sulphite compound. Recrystallised from 50% alcohol it had m. p. and mixed m. p. 130°.

(*c*) *p*-Phenylsulphonylbenzanilide (16·8 g.) (Newell, *loc. cit.*), phosphorus pentachloride (10·5 g.), and tetrachloroethane (60 c.c.) were heated under reflux at 140° for 1 hour. After removal of phosphoryl chloride under reduced pressure the residual imino-chloride, redissolved in the minimum volume of tetrachloroethane, was added to Stephen's reagent (from 40 g. of anhydrous stannous chloride). The mixture was shaken for 2 hours and then kept overnight. The resulting crystalline stannichloride was decomposed by warm 2N-hydrochloric acid, and the aldehyde (7 g.) crystallised from benzene, m. p. 128—130°.

4-p-*Chlorophenylsulphonylbenzaldehyde*.—*p*-Chlorophenyl *p*-tolyl sulphone (20 g.) was oxidised with chromic oxide (20 g.) in acetic acid (150 c.c.), acetic anhydride (150 c.c.), and concentrated sulphuric acid (17 c.c.) as described for the phenylsulphonyl analogue. The intermediate 4-p-*chlorophenylsulphonylbenzylidene diacetate* crystallised from alcohol in colourless prisms, m. p. 152° (Found: C, 53·5; H, 4·1; S, 8·3. $C_{17}H_{15}O_4ClS$ requires C, 53·6; H, 3·9; S, 8·3%). Hydrolysis of the crude diacetate gave the free *aldehyde* (15 g.) which when recrystallised from benzene—light petroleum had m. p. 154° (Found: C, 55·4; H, 3·4. $C_{13}H_9O_3ClS$ requires C, 55·6; H, 3·2%), depressed to 130° by admixture with the diacetate.

4-p-*Methoxyphenylsulphonylbenzaldehyde*.—(*a*) The crude intermediate diacetate, which contained an

appreciable amount of unchanged starting material, obtained as above from *p*-methoxyphenyl *p*-tolyl sulphone (19 g.), was hydrolysed, and the *aldehyde* (2 g.) purified from a solution in chloroform through its sodium hydrogen sulphite compound and then by crystallisation from benzene–light petroleum; m. p. 133—134° (Found: C, 60·7; H, 4·4. $C_{14}H_{12}O_4S$ requires C, 60·9; H, 4·4%).

(*b*) A solution of *p*-methoxyphenyl *p*-tolyl sulphone (8 g.) in chloroform (10 c.c.) was added slowly to chromyl chloride (7 g.) in chloroform (10 c.c.); there was no immediate reaction, but slow separation of a precipitate, accompanied by evolution of heat, occurred. The mixture was shaken frequently for 2 hours and then refluxed on the steam-bath for 1 hour; the colour changed to deep brown and more solid separated. After standing overnight the product was treated with excess of aqueous sulphur dioxide and the chloroform evaporated. The aldehyde (1 g.), purified as in (*a*), had m. p. and mixed m. p. 133°.

Application of either of these procedures to 3 : 4-dimethoxyphenyl *p*-tolyl sulphone gave unchanged material as the only solid product. When this sulphone (5 g.) was oxidised with boiling aqueous potassium permanganate (6 g.), unchanged material (3·5 g.) was extracted from the manganese dioxide cake left on filtration. Acidification of the filtrate gave carbon dioxide and a little *4-3′ : 4′-dimethoxyphenylsulphonylbenzoic acid* (0·5 g.), which separated from dilute acetic acid as an amorphous powder, m. p. 273° (Found: C, 55·5; H, 4·6. $C_{15}H_{14}O_6S$ requires C, 55·9; H, 4·3%).

p-*Sulphamylbenzaldehyde.*—(*a*) *p*-Toluenesulphonamide (12 g.) was oxidised with chromic oxide (15 g.) in a mixture of acetic acid (100 c.c.), acetic anhydride (100 c.c.), and concentrated sulphuric acid (17 c.c.); after all the oxide had dissolved, benzene (100 c.c.) and light petroleum (50 c.c.) were added. The precipitated dark green sticky solid was suspended in water, and adhering acid neutralised by a little solid sodium hydrogen carbonate. The product was hydrolysed by refluxing with alcohol (10 c.c.), water (10 c.c.), and concentrated sulphuric acid (2 c.c.). The *aldehyde* (4 g.) separated from water in transparent prisms, m. p. 118—120° (Found: C, 45·5; H, 4·1. $C_7H_7O_3NS$ requires C, 45·4; H, 3·9%).

(*b*) Finely powdered *p*-cyanobenzenesulphonamide (15 g.) suspended in dry ether (200 c.c.) was saturated with dry hydrogen chloride and then added to Stephen's reagent from anhydrous stannous chloride (30 g.) in ether (300 c.c.). The mixture was shaken for 6 hours, and after being kept overnight the colourless stannichloride was decomposed with warm, dilute hydrochloric acid (50 c.c.). The aldehyde separated when the solution was cooled, and was recrystallised from water; m. p. and mixed m. p. 118—120°.

p-*Methylthioacetophenone.*—Acetic anhydride (8 g.) was added gradually with stirring to a gently boiling mixture of thioanisole (12·4 g.), carbon disulphide (40 c.c.), and anhydrous aluminium chloride (26·7 g.). The resulting green solution was boiled for 1 hour, the carbon disulphide distilled off, and the viscous residue poured while still warm into vigorously stirred ice-cold dilute hydrochloric acid. The resulting mixture was heated on the steam-bath for ½ hour, cooled, and the p-*methylthioacetophenone* crystallised from alcohol. It separated in colourless prisms, m. p. 80° (yield 14 g.) (Found: C, 65·0; H, 6·0. $C_9H_{10}OS$ requires C, 65·1; H, 6·0%).

p-*Methylsulphonylacetophenone.*—(*a*) *p*-Methylthioacetophenone (4 g.) in acetic acid (10 c.c.) was oxidised with 30% hydrogen peroxide (15 c.c.) at 100° for ½ hour. Evaporation to a small volume gave, on cooling, colourless prisms, m. p. 126°, unchanged by recrystallisation from alcohol.

(*b*) *p*-Methylsulphonylbenzonitrile (5·5 g.) in warm benzene (130 c.c.) was added gradually with, stirring to methylmagnesium iodide from magnesium (2·8 g.), methyl iodide (16·5 g.), and ether (60 c.c.) A yellow gelatinous precipitate formed immediately. The mixture was stirred for 1 hour, refluxed for a further 18 hours, and after being kept overnight was poured slowly on ice (200 g.) and concentrated sulphuric acid (60 c.c.). After 2 hours' heating at 100° under reflux, the benzene and aqueous layers were filtered from some insoluble, tarry solid (*A*). The benzene layer was combined with the benzene extract of the aqueous solution, then washed successively with dilute sodium hydroxide and water. The dried (Na_2SO_4) benzene solution was concentrated and ligroin then added; crystals contaminated with a little tar separated. Recrystallisation from alcohol (charcoal) gave the ketone (1 g.), m. p. 126°, unchanged by admixture with that prepared under (*a*) (Fuller, Tonkin, and Walker, *loc. cit.*, give m. p. 128—129°) (Found: C, 54·4; H, 5·0. Calc. for $C_9H_{10}O_3S$: C, 54·5; H, 5·0%).

The tarry solid (*A*), which had m. p. *ca.* 100°, was obviously largely unchanged nitrile since it was hydrolysed by sodium hydroxide to *p*-methylsulphonylbenzoic acid, m. p. 265—267°, after crystallisation from alcohol.

p-*Phenylsulphonylacetophenone.*—*p*-Phenylsulphonylbenzonitrile (12 g.) in benzene (100 c.c.) was added with striring to the Grignard reagent from magnesium (4·8 g.), methyl iodide (28·4 g.), and ether (50 c.c.). After 3 hours' stirring, benzene (100 c.c.) was added, and the mixture refluxed for 20 hours. Decomposition as above (filtration not being necessary) gave the *ketone* (8 g.) which crystallised from benzene in almost colourless prisms, m. p. 136—137° (Found: C, 64·4; H, 4·6. $C_{14}H_{12}O_3S$ requires C, 64·6; H, 4·6%).

p-*Methylsulphonylbenzophenone.*—*p*-Methylsulphonylbenzonitrile (9 g.) in benzene (200 c.c.) with the Grignard reagent from magnesium (4·8 g.), bromobenzene (31·4 g.), and ether (100 c.c.) gave, after being refluxed for 16 hours and then decomposed as above, the *ketone* (10 g.) which separated from benzene–ligroin in nearly colourless plates, m. p. 134—136° (Found: C, 65·0; H, 4·6. $C_{14}H_{12}O_3S$ requires C, 64·6; H, 4·6%).

p-*Phenylsulphonylbenzophenone.*—Finely powdered, anhydrous aluminium chloride (5 g.) was added gradually to *p*-phenylsulphonylbenzoyl chloride (10 g.) in benzene (30 c.c.) at 75°. The mixture was then heated, with frequent shaking, at 85—90° for 2 hours, and, after cooling, decomposed with dilute hydrochloric acid. The excess of benzene was evaporated and the resulting solid product washed with dilute hydrochloric acid and then heated with dilute sodium hydroxide at 100 for 1 hour. The *ketone* (8 g.) crystallised from alcohol in colourless prisms, m. p. 144° (Found: C, 70·3; H, 4·5. $C_{19}H_{14}O_3S$ requires C, 70·8; H, 4·4%).

Our thanks are due to the British Council for a scholarship to one of us (P. F. H.).

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125. p-*Methylthiobenzenesulphonyl Chloride and Related Compounds.*

By H. Burton and P. F. Hu.

Thioanisole with chlorosulphonic acid gave the *p*-sulphonyl chloride which was a useful intermediate for the preparation of *p*-derivatives containing sulphur in both groups.

We have shown (previous paper) that thioanisole undergoes the Friedel–Crafts reaction to give *p*-methylthioacetophenone, and we now report the successful introduction of the sulphonyl chloride group—also into the *p*-position. The resulting p-*methylthiobenzenesulphonyl chloride* (I) was utilised for the preparation of *p-methylthio- and* thence p-*methylsulphonylbenzenesulphonamide* and also of p-*methylthiobenzenesulphinic acid* (II). The last compound (as the sodium salt) was converted by methyl iodide into p-*methylsulphonylthioanisole* (III) which was also obtained by methylation of *p*-methylsulphonylthiophenol, in turn prepared from *p*-methylsulphonylaniline (*p*-aminophenyl methyl sulphone) by the diazo-reaction. These results confirm the structure of (I). p-*Bismethylsulphonylbenzene* was readily obtained by oxidation of (III).

The production of (III) from (II) is an example of the well-known method of synthesis of sulphones, $R{\cdot}SO_2R'$, whereby an alkali or silver sulphinate, $R{\cdot}SO_2M$, is treated with a reactive halide, R'Hal. Steinkopf (Houben's "Methoden der Org. Chem.", 1930, Vol. 3, 1325) consequently postulates the structure of a sulphinic acid as either R·S·H or $R{\cdot}\overset{\overset{O}{\|}}{S}{\cdot}OH$. This dual mode of representing the structure appears to be quite unnecessary especially as the sulphinate ion is undoubtedly $R{\cdot}\overset{\ominus}{S(O)}{\cdot}O$. The group introduced would be co-ordinated either to sulphur (as is usually the case) or to oxygen, and would parallel the alkylation of ethyl acetoacetate.

Todd and Shriner (*J. Amer. Chem. Soc.*, 1934, **56**, 1382) have shown that the activating effect of the methylsulphonyl group on halogen is not nearly so great as that of the nitro-group in the reaction with alcoholic sodium ethoxide. We have confirmed this in the behaviour of *p*-chlorophenyl methyl sulphone towards sodium disulphide. Reaction proceeded much less readily than with *p*-chloronitrobenzene, and under the reaction conditions used we obtained only 4 : 4'-*bismethylsulphonyldiphenyl sulphide*; a careful search for any disulphide failed to reveal more than a trace. This sulphide was characterised further by oxidation to the *trisulphone*.

Experimental.

p-*Methylthiobenzenesulphonyl Chloride*.—Chlorosulphonic acid (25 g.) was added dropwise with stirring to a solution of thioanisole (5 g.) in chloroform (20 c.c.) at such a rate that the temperature did not exceed 5°. After the intital evolution of hydrogen chloride had subsided the mixture was stirred at room temperature, and further evolution of hydrogen chloride occurred. The mixture was then poured with vigorous stirring on crushed ice (100 g.), and the chloroform layer (*A*) subsequently separated, wasted with a little ice-cold water, and dried (Na_2SO_4). Evaporation gave a viscous oil which solidified when kept. Crystallisation of this solid, m. p. 42—43°, from benzene–ligroin gave colourless prisms of the *sulphonyl chloride* (7·5 g.), m. p. 44—45° (Found: C, 38·1; H, 3·4. $C_7H_7O_2ClS_2$ requires C, 37·7; H, 3·2%).

When the chloroform solution (*A*) was treated with ammonium carbonate (10 g.), the mixture evaporated to dryness on the steam-bath, and the crystalline residue washed repeatedly with cold water, p-*methylthiobenzenesulphonamide* remained insoluble. It separated from alcohol in colourless prisms (6·5 g.), m. p. 164—165° (Found: C, 41·4; H, 4·4; S, 32·4. $C_7H_9O_2NS_2$ requires C, 41·4; H, 4·4; S, 31·7%).

This amide was oxidised by 30% hydrogen peroxide in acetic acid at 100° to p-*methylsulphonylbenzenesulphonamide*, colourless prisms from alcohol, m. p. 236° (Found: S, 27·4. $C_7H_9O_4NS_2$ requires S, 27·2%).

p-*Methylthiobenzenesulphinic Acid*.—Finely powdered *p*-methylthiobenzenesulphonyl chloride (5 g.) was shaken with a solution of sodium sulphite heptahydrate (7 g.) in water (30 c.c.), the mixture being kept slightly alkaline (phenolphthalein) by addition of 50% sodium hydroxide. After 2 hours a little insoluble matter was removed and the filtrate kept overnight in the refrigerator. The crystalline inorganic matter was filtered off and washed with a little ice-cold water, and the combined filtrate and washings were acidified (Congo-red) with 60% sulphuric acid. Colourless needles separated; crystallisation from dilute alcohol gave the *sulphinic acid* (3·5 g.), m. p. 91—92° (Found: C, 44·5; H, 3·9. $C_7H_8O_2S_2$ requires C, 44·7; H, 4·25%).

p-*Methylsulphonylthioanisole*.—(*a*) *p*-Methylsulphonylaniline hydrochloride (Goldberg and Besly, *J.*, 1945, 568) (8·3 g.) was diazotised with sodium nitrite (2·8 g.) in N-hydrochloric acid (40 c.c.) and then treated with sodium acetate trihydrate (5·2 g.). This solution was then added gradually with stirring to potassium ethyl xanthate (12 g.) in water (28 c.c.) at 70—80° and maintained at this temperature for 1½ hours. The solid product, combined with the ethereal extract of the aqueous filtrate, was refluxed with alcohol (80 c.c.) containing potassium hydroxide (4·6 g.) and glucose (4·6 g.), and the alcohol removed

by distillation. Dilute sulphuric acid precipitated a solid product, together with some oil, when added to the residue. The solid, after drying on porous earthenware, crystallised from acetic acid in nearly colourless plates, and was 4 : 4′-*bismethylsulphonyldiphenyl disulphide* (4 g.), m. p. 188° (Found: C, 44·4; H, 3·9. $C_{14}H_{14}O_4S_4$ requires C, 44·9; H, 3·7%). The disulphide was also obtained by oxidation of the oil (free thiol) with ferric chloride in acetic acid. Methylation of the thiol with methyl sulphate in 2N-sodium hydroxide first below 10° and then at 95° gave p-*methylsulphonylthioanisole*, colourless prisms from alcohol, m. p. 98—99° (Found: C, 47·9; H, 5·2. $C_8H_{10}O_2S_2$ requires C, 47·5; H, 5·0%).

(*b*) *p*-Methylthiobenzenesulphinic acid (2 g.) was neutralised with 2N-sodium hydroxide and alcohol (5 c.c.), and methyl iodide (2 c.c.) added. The mixture was refluxed for 14 hours and volatile products distilled. Cooling and addition of water precipitated the compound (1·5 g.), which when crystallised from alcohol had m. p. and mixed m. p. 98—99°.

p-*Bismethylsulphonylbenzene.*—*p*-Methylsulphonylthioanisole (1·5 g.) in acetic acid (10 c.c.) was heated with 30% hydrogen peroxide (8 c.c.) at 100° for ½ hour. Colourless plates of the *disulphone* (1 g.) separated on cooling; these had m. p. 256° after crystallisation from alcohol (Found: C, 41·0; H, 4·3. $C_8H_{10}O_4S_2$ requires C, 41·0; H, 4·3%).

4 : 4′-*Bismethylsulphonyldiphenyl Sulphone.*—*p*-Chlorophenyl methyl sulphone, prepared from sodium *p*-chlorobenzenesulphinate and methyl iodide (as above), crystallised from alcohol in colourless needles, m. p. 96° (Miller and Smiles, *J.*, 1925, **127**, 224, give m. p. 96°, whilst Purgotti, *Chem. Abs.*, 1919, **13**, 2515, gives m. p. 57—58°).

This sulphone (10 g.) was added to sodium disulphide, made by heating crystalline sodium sulphide (11 g.) with sulphur (1·5 g.) until a clear solution resulted, and the mixture kept at 150—160° (bath temp.) for 20 hours. The mass was treated with warm water and the insoluble solid crystallised from acetic acid. 4 : 4′-*Bismethylsulphonyldiphenyl sulphide* (6 g.) formed small, colourless, shining plates, m. p. 196—197° (Found: C, 49·0; H, 4·2. $C_{14}H_{14}O_4S_3$ requires C, 49·1; H, 4·1%). No reaction occurred below 140°.

Oxidation with 30% hydrogen peroxide in acetic acid at 100° for ½ hour gave the crystalline *trisulphone*, which did not melt below 308°, and was insoluble in the usual common solvents (Found: C, 44·6; H, 3·9; S, 25·4. $C_{14}H_{14}O_6S_3$ requires C, 44·9; H, 3·8; S, 25·7%).

We thank the British Council for a scholarship to one of us (P. F. H.).

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126. *Experiments with Diazomethane and its Derivatives. Part XIV. Action of Diazomethane on* (a) N-*Acyl Compounds and* (b) o-*Hydroxydiaryl Sulphones and the Corresponding* peri-*Compounds.*

By ALEXANDER SCHÖNBERG and AHMED MUSTAFA.

It was found that certain *N*-diacyl compounds are stable towards ethereal diazomethane but are converted into the corresponding monoacyl compounds by an ether–methyl alcoholic diazomethane solution.

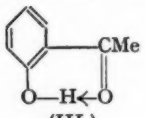
o-Hydroxydiaryl sulphones (in contrast to many *o*-hydroxydiaryl ketones) can be converted into the corresponding methoxy-derivatives by the action of ethereal diazomethane.

(*a*) SCHÖNBERG and MUSTAFA (*J.*, 1946, 746) found that diazomethane in a mixture of ether and an aliphatic alcohol forms an addition product (*e.g.*, I*a* or I*b*) which has powerful alkylating properties. For instance, with *n*-propyl alcohol the di-*n*-propyl ether of stilboestrol is produced, and in methyl alcohol benzophenone oxime can be methylated, whereas it is unaffected by *ethereal* diazomethane. We now show that diazomethane in ether–methyl alcohol quantitatively converts *N*-diacetyl-α- or -β-naphthylamine, -aniline, or -*p*-toluidine, or *N*-dibenzoyl-aniline or -α-naphthylamine into the corresponding monoacyl compounds. The *N*-diacyl compounds are stable to ether, to a mixture of ether and methyl alcohol, or to ethereal diazomethane under the experimental conditions used (24 hours in the cold): reaction takes place only with diazomethane in a mixture of ether and alcohol. It is believed that the reaction proceeds according to the following scheme, in which (II) is hypothetical.

$$\underset{(Ia.)}{CH_3{\cdot}N{:}N{\cdot}OMe} \rightleftharpoons \underset{(Ib.)}{CH_2{:}N{\cdot}NH{\cdot}OMe} + NPhAc_2 \longrightarrow Ph{\cdot}NHAc + \underset{(II.)}{CH_2{:}N{\cdot}NAc{\cdot}OMe}$$

(*b*) It is known that many *o*-hydroxy-ketones (Schönberg and Mustafa, *loc. cit.*) do not react with ethereal diazomethane but are methylated by diazomethane in an ether–alcohol medium. This is due, not only to the formation of an alkylating agent (*e.g.*, I*a* and I*b*), but also to the fact that by the action of methyl alcohol the chelated ring systems are opened (*e.g.*, III and IV). We were interested to discover whether *o*-hydroxydiaryl sulphones as well as the corresponding *peri*-compounds are capable of reacting with diazomethane even in the absence of alcohol; this is indeed the case with (VI) and (VII; R = Ph or α-naphthyl). This fact

may be interpreted in two ways : either there is no chelation at all in these compounds, or the ring formed by chelation is easily broken. Reference should be made to formula (V) (cf. Gilman " Organic Chemistry, An Advanced Treatise ", 2nd edtn., p. 1870, New York, 1944).



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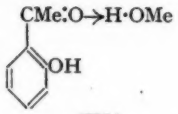

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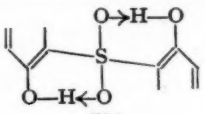

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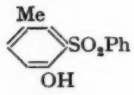

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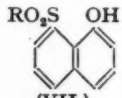
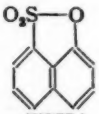


(VII.)



(VIII.)

1-Hydroxy-8-phenylsulphonylnaphthalene (VII, R = Ph) and 1-hydroxy-8-α-naphthylsulphonylnaphthalene (VII, R = $C_{10}H_7$) were synthesised by the action of phenyl- and α-naphthyl-magnesium bromide respectively on naphthasultone (VIII), followed by hydrolysis. (This method will be described in detail later.) Phenyl 4-hydroxy-*m*-tolyl sulphone (VI) was obtained in a similar manner from tolylene-3 : 4-sulphonylide (Anschütz, *Annalen*, 1918, **415**, 76).

We found that naphthasultam (VIII, but with NH instead of O) is converted into the *N*-methyl derivative by the action of diazomethane in ether (for the *N*-methylation of saccharin and related substances, see Schönberg *et al.*, *Ber.*, 1933, **66**, 244).

Experimental.

Action of Ethereal Diazomethane in the Presence or in the Absence of Methyl Alcohol on N-*Diacetylamines and on Acet-α-naphthalide.*—(i) The ethereal diazomethane solution was prepared by reaction between aqueous potassium hydroxide and a suspension of nitrosomethylurea (8 g.), followed by distillation of the ether and diazomethane (*Org. Synth.*, **15**, 3). The ethereal distillate containing the diazomethane was divided into two equal portions of 55 c.c. In each portion *N*-diacetyl-α-naphthylamine (0·1 g.) was dissolved, and to one solution methyl alcohol (5 c.c.) was added ; both were then kept in an ice-chest overnight. The solution containing methyl alcohol afforded acet-α-naphthalide (m. p. and mixed m. p.) in quantitative yield, whereas the other afforded the diacetyl derivative (m. p. and mixed m. p.).

(ii) Precisely similar experiments with acet-α-naphthalide led to its recovery unchanged in each case.

(iii) A solution of *N*-diacetyl-α-naphthylamine in ether–methyl alcohol of the above composition was unchanged after 24 hours in an ice-chest.

(iv) By the procedure described for *N*-diacetyl-α-naphthylamine [(i) above], the other five diacyl compounds mentioned on p. 605 were quantitatively transformed into monoacyl derivatives (identified by m. p. and mixed m. p.).

Action of Ethereal Diazomethane Solution on N-*Diacetyl-α-naphthylamine in the Presence of* n-*Propyl Alcohol.*—The experiment (first paragraph) was repeated but with *n*-propyl alcohol (5 c.c.) in place of methyl alcohol. Acet-α-naphthalide (m. p. and mixed m. p.) was obtained in quantitative yield.

Action of Ethereal Diazomethane on o-*Hydroxydiaryl Sulphones and the Corresponding* peri-*Compounds.*—(i) Phenyl 4-hydroxy-*m*-tolyl sulphone (VI) was allowed to react with ethereal diazomethane, prepared as above, for 24 hours at 0°. The reaction product was evaporated to dryness, and an ethereal solution of the residue was treated with aqueous potassium hydroxide (to remove unchanged VI) and then with water, dried (Na_2SO_4), and the ether evaporated at room temperature. Phenyl 4-methoxy-*m*-tolyl sulphone crystallised from benzene–light petroleum (b. p. 50—70°) as colourless crystals, m. p. 139°, insoluble in aqueous sodium hydroxide (Found : C, 63·7; H, 5·5; S, 12·2. Calc. for $C_{14}H_{14}O_3S$: C, 64·1; H, 5·3; S, 12·2%). Heppenstall and Smiles (*J.*, 1938, 899) gave m. p. 137—138°.

(ii) 1-*Methoxy*-8-*phenylsulphonylnaphthalene* was obtained from 1-hydroxy-8-phenylsulphonylnaphthalene (VII, R = Ph) by the above method in colourless crystals, m. p. 165°, from benzene–light petroleum (b. p. 50—70°) ; they were insoluble in aqueous sodium hydroxide and gave no colour reaction with sulphuric acid (Found : C, 68·3; H, 4·6; S, 10·7. $C_{17}H_{14}O_3S$ requires C, 68·5; H, 4·7; S, 10·7%).

(iii) 1-*Methoxy*-8-*α-naphthylsulphonylnaphthalene* was obtained similarly from 1-hydroxy-8-α-naphthylsulphonylnaphthalene (VII, R = $C_{10}H_7$) as colourless crystals, m. p. 220°, from benzene–light petroleum (b. p. 50—70°) ; they were insoluble in hot aqueous sodium hydroxide (Found : C, 72·2; H, 4·6; S, 8·9; OMe, 8·5. $C_{21}H_{14}O_3S$ requires C, 72·4; H, 4·6; S, 9·2; OMe, 8·9%).

Action of Ethereal Diazomethane on 1 : 8-*Naphthasultam.*—*N*-Methylnaphthasultam was similarly obtained by the action of ethereal diazomethane on naphthasultam (Dannerth, *J. Amer. Chem. Soc.*, 1907, **29**, 1319) as colourless crystals, m. p. 125—126°, from benzene–light petroleum (b. p. 50—70°). It was soluble in hot ethyl alcohol with a greenish-violet fluorescence and gave a violet fluorescence with sulphuric acid after some time (Found : C, 60·4; H, 4·4; N, 6·0; S, 14·3. Calc. for $C_{11}H_9O_2NS$: C, 60·2; H, 4·1; N, 6·4; S, 14·6%). Dannerth (*loc. cit.*) gave m. p. 125°.

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127. *Physical Properties and Chemical Constitution. Part X.* n-*Alkylbenzenes.*

By Arthur I. Vogel.

n-Alkylbenzenes (toluene to *n*-hexylbenzene) have been prepared in a high degree of purity and their parachors and refractivities measured. The data give for CH_2: P 39·2, R_C 4·625, R_D 4·645, R_F 4·699, $R_{G'}$ 4·734, and $Mn_D^{20°}$ 20·66.

The normal alkylbenzenes have been prepared, with one exception, by Clemmensen reduction of the appropriate purified keto-compounds as follows: toluene from benzaldehyde; ethylbenzene from acetophenone; *n*-propylbenzene from propiophenone and from benzyl methyl ketone * and also from benzylmagnesium chloride and ethyl sulphate; *n*-butylbenzene from butyrophenone and from benzyl ethyl ketone *; *n*-amylbenzene from valerophenone and from benzyl *n*-propyl ketone *; *n*-hexylbenzene from 2-phenylethyl *n*-propyl ketone. Where more than one method of preparation has been employed, the procedure considered to give the purest product has been indicated by an asterisk. The parachors and refractivities have been determined. The results are summarised in the following table; molecular refractivities refer to a temperature of 20°. The mean values of the CH_2 increment have been calculated by the method of least squares. The final values given in Part IX (*J.*, 1946, 133) from the data on *n*-aliphatic hydrocarbons and *n*-alkyl halides were P 40·0, R_C 4·624, R_D 4·647, R_F 4·695, $R_{G'}$ 4·735, and $Mn_D^{20°}$ 20·59.

Parachors and refractivities of normal alkylbenzenes.

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
$C_6H_5 \cdot CH_3$	245·4	30·86	31·10	31·70	32·19	137·89
$C_6H_5 \cdot CH_2 \cdot CH_3$	284·3	35·49	35·75	36·41	37·03	158·82
$C_6H_5 \cdot [CH_2]_2 \cdot CH_3$	323·2	40·15	40·43	41·16	41·73	179·29
$C_6H_5 \cdot [CH_2]_3 \cdot CH_3$	362·0	44·78	45·08	45·85	46·47	199·92
$C_6H_5 \cdot [CH_2]_4 \cdot CH_3$	402·0	49·40	49·73	50·56	51·21	220·64
$C_6H_5 \cdot [CH_2]_5 \cdot CH_3$	441·5	53·95	54·29	55·15	55·86	241·35

Mean values for CH_2 *calculated by the method of least squares.*

CH_2	39·2	4·625	4·645	4·699	4·734	20·66

The present communication forms one of a series, the objects of which include: (1) The provision of trustworthy data (parachors and refractivities) for various classes of compounds specifically selected in the first instance for the calculation of atomic, group, and structural constants. (2) The evaluation of atomic, group, and structural constants with particular reference to the parachor and to the refractivities for the C, D, F, and G′ lines. (3) The evaluation of the refractions of electron bonds and electron groups according to von Steiger (*Ber.*, 1921, **54**, 1381), Smyth (*Phil. Mag.*, 1925, **50**, 715; "Dielectric Constant and Molecular Structure," 1931, 150), and Fajans and Knorr (*Ber.*, 1926, **59**, 249), and of bond refractions after the procedure of Denbigh (*Trans. Faraday Soc.*, 1940, **36**, 397). (4) The application of such constants, based exclusively upon the author's own measurements, to structural and constitutional problems.

The mean values of the refractivities for CH_2 given in Part IX (*loc. cit.*) lead to the following refractions for the C–H bond (in CH_2) and the C–C bond at 20°:

	R_C.	R_D.	R_F.	$R_{G'}$.
C–H (in CH_2)	1·669	1·676	1·693	1·704
C–C	1·286	1·296	1·301	1·328

These figures will form the basis of all calculations of bond refractions. For C–H and C–C respectively Smyth (*loc. cit.*) gives 1·705 and 1·209, whilst Fajans and Knorr (*loc. cit.*) deduce 1·704 and 1·209: these values presumably refer to the D sodium line. Since these fundamental constants are clearly in error, all their calculations of the refractions of electron groups must be regarded as very approximate. Denbigh (*loc. cit.*) calculates 1·69 for C–H and 1·25 for C–C directly from the molecular refractions.

* The numbering of compounds in Clarendon type follows from Part IX (*J.*, 1946, 135). Reference to compounds, the preparation of which is described in preceding or succeeding papers of this series, will be abbreviated to, *e.g.*, IX, **101**.

Experimental.

Physical Measurements.—Full details applying to this and the subsequent papers of this series are given in Part VII (*J.*, 1943, 18). Surface tensions were measured by the method of capillary rise, and only the values for H ($= h - 0{\cdot}24$ mm.) are given. The constants for the various apparatus are: *A* 1·8725, *B* 2·3449, *C*, 2·3740, *D* 2·4696, *E* 2·3290. Unless otherwise stated, all b. p.s are corrected. All measurements of the refractive indices were made at 20° ± 0·02° on a Zeiss Pulfrich refractometer. It should be pointed out that measurements upon aromatic compounds, *e.g.*, phenyl alkyl ketones (following paper), phenyl alkyl ethers (Part XII, this vol., p. 616), and even upon alkylbenzenes, especially for the lower homologues, are frequently difficult because of the small separation of the lines with the prism IIf employed: the G′ line is often very faint and adjustment to the crosswires is not a precise operation. The values for $n_{G'}$, in some cases, may, in consequence, be subject to appreciable error. This difficulty of measurement is absent in the new Hilger–Chance refractometer, and it is hoped to repeat the measurements when the instrument is available commercially.

In the tabulated results, t is the temperature, h is the observed difference in height (in mm.) in the two arms of the U-tube, H ($= h - 0{\cdot}24$) is the corrected value, d_4^t, the density (calculated from the observed densities by assuming a linear variation with temperature), γ the surface tension (dynes/cm.) computed from the equation $\gamma = KHd$, P the parachor, M the molecular weight, and $Mn_D^{20°}$ the molecular refraction coefficient. The parachor was calculated in the usual way, allowance for the density of the vapour (computed by Sugden's method, *J.*, 1925, **127**, 1540) being made when the temperature of the measurement was within 60° of the b. p. Where 20° is used, 20·0° is to be understood; n_C, n_D, n_F, $n_{G'}$ are to be taken as referring to $n_C^{20·0°}$, etc.; and R_C, etc. to $[R_L]_C$. Unless otherwise stated, all b. p.s are corrected.

Previous Work.—The larger proportion of the measurements described in this and succeeding papers of this series are new. The constants deduced will in all cases be based upon the author's own measurements. In order to economise space no reference will be made (save in exceptional circumstances) to previous work, since these can be readily found in I.C.T., Landolt–Börnstein "Tabellen", or the original literature.

117.* *Toluene.*—100 G. of purified and redistilled benzaldehyde, b. p. 179°/757 mm., were reduced with 200 g. of amalgamated zinc and concentrated hydrochloric acid (IX, **101**); the yield of crude toluene was 43 g. of b. p. 109—110°/748 mm. This was washed with 10% of its volume of concentrated sulphuric acid until the washings were colourless (two washings required), then successively with water, 10% sodium carbonate solution, and water, and finally dried ($MgSO_4$). It was then *twice* distilled from sodium and passed over constantly in the second distillation at 110°/763 mm.; a middle fraction was used for the physical measurements.

B. p. 110°/763 mm.; M 92·13; n_C 1·49216, n_D 1·49669, n_F 1·50817, $n_{G'}$ 1·51743; R_C 30·86, R_D 31·10, R_F 31·70, $R_{G'}$ 32·19; $Mn_D^{20°}$ 137·89. Densities determined: $d_4^{20°}$ 0·8665, $d_4^{41·0°}$ 0·8483, $d_4^{60·0°}$ 0·8310, $d_4^{86·0°}$ 0·8071. Apparatus *A*.

(These headings apply to the corresponding columns in all the following tables.)

t.	H.	d_4^t.	γ.	P.	t.	H.	d_4^t.	γ.	P.
18·7°	17·68	0·8675	28·72	245·9	60·8°	15·27	0·8303	23·74	245·0
24·9	17·35	0·8621	28·01	245·8	86·4	13·84	0·8067	20·91	244·8
41·2	16·38	0·8481	26·01	245·3				Mean	245·4

118. *Ethylbenzene.*—100 G. of acetophenone, b. p. 200°/760 mm., when reduced as above, yielded 53 g. of crude ethylbenzene, b. p. 134·5—135°/758 mm. This was shaken with 6-ml. portions of concentrated sulphuric acid until the acid layer was colourless, and the pure hydrocarbon was isolated as detailed under toluene.

B. p. 135°/755 mm.; M 106·16; n_C 1·49170, n_D 1·49598, n_F 1·50686, $n_{G'}$ 1·51567; R_C 35·49, R_D 35·75, R_F 36·41, $R_{G'}$ 37·03; $Mn_D^{20°}$ 158·82. Densities determined: $d_4^{20°}$ 0·8675, $d_4^{41·0°}$ 0·8494, $d_4^{61·0°}$ 0·8321, $d_4^{85·5°}$ 0·8106. Apparatus *D*.

15·6°	13·72	0·8713	29·52	284·0	60·9	12·00	0·8322	24·66	284·3
22·1	13·55	0·8657	28·97	284·5	85·4	11·11	0·8107	22·44	284·4
40·5	12·80	0·8498	26·86	284·4				Mean	284·3

119. n-*Propylbenzene.* *Method* 1.—This was prepared from benzyl chloride, b. p. 177—179°/757 mm., magnesium, and purified ethyl sulphate according to *Org. Synth.*, Coll. Vol. I, 1932, 458, with the modification that the crude product (100 g.), after drying over potassium hydroxide pellets, was distilled from sodium through a lagged three-section Pyrex Young and Thomas fractionating column; 60 g. of *n*-propylbenzene, b. p. 156—158°/756 mm., were obtained and there was a considerable residue in the flask. Upon redistillation from sodium, this boiled largely at 158—158·5°/771 mm. and a middle fraction had $d_4^{20°}$ 0·8649, $n_D^{20°}$ 1·49338. The resulting hydrocarbon was washed with 8-ml. portions of concentrated sulphuric acid until the acid layer was colourless (3 washings), and the pure *n*-propylbenzene isolated as under toluene.

B. p. 158·5°/760 mm.; M 120·19; n_C 1·48904, n_D 1·49313, n_F 1·50283, $n_{G'}$ 1·51194; R_C 40·13, R_D 40·42, R_F 41·09, $R_{G'}$ 41·72; $Mn_D^{20°}$ 179·46. Densities determined: $d_4^{20°}$ 0·8643, $d_4^{40·5°}$ 0·8473, $d_4^{60·4°}$ 0·8310, $d_4^{84·6°}$ 0·8109. Apparatus *A*.

15·1°	18·26	0·8684	29·69	323·1	59·7	16·12	0·8316	25·10	323·5
22·5	17·97	0·8622	29·01	323·5	85·3	14·82	0·8103	22·49	323·0
41·3	16·99	0·8463	26·92	323·5				Mean	323·3

Method 2. 100 G. of propiophenone (XI, **139**), reduced as for toluene, afforded, after steam distillation, 64 g. of crude *n*-propylbenzene; the viscid liquid residue in the flask probably consisted largely of phenylethylcarbinol. Upon redistillation from sodium through a Pyrex Young and Thomas column about 90% distilled at 160—165°/764 mm. (mainly at 160—162°) and evidently contained an appreciable quantity of an unsaturated hydrocarbon (allyl- and/or propenyl-benzene). This was washed with 10% of its volume of concentrated sulphuric acid until the acid layer was colourless (at least 10 washings; loss about 30%) and the pure hydrocarbon was isolated as under toluene.

B. p. 157·5°/763 mm.; M 120·19; n_C 1·48805, n_D 1·49215, n_F 1·50243, $n_{G'}$ 1·51070; R_C 40·21, R_D 40·50, R_F 41·21, $R_{G'}$ 41·78; $Mn_D^{20°}$ 179·35. Densities determined: $d_{4°}^{20°}$ 0·8613, $d_{4°}^{42·0°}$ 0·8434, $d_{4°}^{60·6°}$ 0·8282, $d_{4°}^{86·0°}$ 0·8072. Apparatus *D*.

t.	*H.*	$d_{4°}^{t°}$.	γ.	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	γ.	*P.*
16·9°	13·63	0·8638	29·08	323·5	60·6°	12·04	0·8282	24·63	323·6
23·6	13·33	0·8584	28·26	323·2	85·9	11·13	0·8073	22·19	323·5
41·2	12·66	0·8440	26·39	323·1				Mean	323·4

Method 3. 75 G. of benzyl methyl ketone (XI, **132**), reduced with amalgamated zinc and concentrated hydrochloric acid, afforded, after steam distillation, 48 g. of the organic product. Upon distillation from sodium, 38 g. of crude *n*-propylbenzene, b. p. 157—162°/770 mm., were obtained; unsaturated hydrocarbons were removed by 20 washings with 4-ml. portions of concentrated sulphuric acid and the pure hydrocarbon was isolated as usual.

B. p. 157·5°/763 mm.; M 120·19; n_C 1·48769, n_D 1·49174, n_F 1·50208, $n_{G'}$ 1·51042; R_C 40·15, R_D 40·43, R_F 41·16, $R_{G'}$ 41·73; $Mn_D^{20°}$ 179·29. Densities determined: $d_{4°}^{20°}$ 0·8620, $d_{4°}^{41·2°}$ 0·8444, $d_{4°}^{61·5°}$ 0·8280, $d_{4°}^{85·7°}$ 0·8079. Apparatus *A*.

17·1°	18·07	0·8644	29·25	323·4	61·8°	15·87	0·8278	24·60	323·4
20·8	17·80	0·8614	28·71	323·0	86·9	14·62	0·8069	22·09	323·0
41·1	16·82	0·8445	26·60	323·2				Mean	323·2

120. iso*Propylbenzene.*—The unsaturated hydrocarbons present in 100 g. of a pure commercial sample were removed by washing 5 times with 10-ml. volumes of concentrated sulphuric acid, the product was washed successively with water, 10% sodium carbonate solution, and water, and dried ($MgSO_4$); it was then fractioned over sodium through a three-section Pyrex Young and Thomas column and the fraction (*ca.* 90%), b. p. 151—152°/760 mm., was collected. This was again distilled over sodium, and a middle fraction collected for the physical measurements.

B. p. 151°/758 mm.; M 120·19; n_C 1·48684, n_D 1·49088, n_F 1·50110, $n_{G'}$ 1·50931; R_C 40·11, R_D 40·39, R_F 41·10, $R_{G'}$ 41·67; $Mn_D^{20°}$ 179·19. Densities determined: $d_{4°}^{20°}$ 0·8616, $d_{4°}^{41·2°}$ 0·8442, $d_{4°}^{61·2°}$ 0·8274, $d_{4°}^{86·7°}$ 0·8058. Apparatus *D*.

13·9°	13·38	0·8667	28·64	320·8	60·9°	11·64	0·8276	23·79	320·7
41·2	12·35	0·8442	25·75	320·7	86·3	10·81	0·8061	21·52	321·1
								Mean	320·8

121. n-*Butylbenzene.*—*Method* 1. 75 G. of butyrophenone, b. p. 227—230°/777 mm. (XI, **140**), were reduced with 150 g. of amalgamated zinc and concentrated hydrochloric acid and yielded, upon steam distillation, 50 g. of an organic product. The crude *n*-butylbenzene, b. p. 181—184°, isolated by distillation from sodium was washed with 7-ml. portions of concentrated sulphuric acid until the acid layer was colourless, and the pure hydrocarbon was isolated as under toluene.

B. p. 181·5°/767 mm.; M 134·21; n_C 1·48577, n_D 1·48960, n_F 1·49948, $n_{G'}$ 1·50743; R_C 44·81, R_D 45·11, R_F 45·88, $R_{G'}$ 46·50; $Mn_D^{20°}$ 199·92. Densities determined: $d_{4°}^{20°}$ 0·8595, $d_{4°}^{41·0°}$ 0·8444, $d_{4°}^{61·6°}$ 0·8281, $d_{4°}^{87·3°}$ 0·8081. Apparatus *D*.

18·5°	13·71	0·8606	29·14	362·3	61·0°	12·21	0·8286	24·99	362·1
24·1	13·58	0·8564	28·72	362·8	87·1	11·43	0·8083	22·82	362·9
41·5	12·88	0·8440	26·85	362·0				Mean	362·4

Method 2. 70 G. of benzyl ethyl ketone, b. p. 113—115°/17 mm. (XI, **133**), were reduced as in the preceding preparation. The crude *n*-butylbenzene, b. p. 180—183°/760 mm., isolated by steam distillation (62 g.) and distillation from sodium, weighed 50 g. This was washed 10 times with 10-ml. portions of concentrated sulphuric acid, and the pure hydrocarbon was obtained after two distillations over sodium in the usual manner.

B. p. 180·5—181°/767 mm.; M 134·21; n_C 1·48567, n_D 1·48955, n_F 1·49942, $n_{G'}$ 1·50738; R_C 44·78, R_D 45·08, R_F 45·85, $R_{G'}$ 46·47; $Mn_D^{20°}$ 199·92. Densities determined: $d_{4°}^{20°}$ 0·8601, $d_{4°}^{41·0°}$ 0·8442, $d_{4°}^{61·2°}$ 0·8283, $d_{4°}^{86·5°}$ 0·8083. Apparatus *A*.

13·6°	18·34	0·8651	29·71	362·2	41·0°	16·98	0·8442	26·84	361·9
20·0	17·99	0·8601	28·97	362·0	60·9	16·01	0·8285	24·84	361·8
25·4	17·76	0·8559	28·46	362·2	87·3	14·85	0·8076	22·46	361·8
								Mean	362·0

122. n-*Amylbenzene.*—*Method* 1. 36 G. of valerophenone, b. p. 104—106°/5 mm., prepared by the reactions

n-Valeric acid (Eastman Kodak) $\xrightarrow{SOCl_2}$ *n*-Valeryl chloride (b. p. 125—127°/758 mm.) $\xrightarrow[(excess)]{AlCl_3;\ C_6H_6}$ Valerophenone

were reduced with 100 g. of amalgamated zinc and concentrated hydrochloric acid. The mixture was steam distilled, and the organic layer (19 g.) was distilled from sodium to give 16 g. of crude *n*-amylbenzene, b. p. 199—203°/768 mm. (mainly 201—202°). This was washed 10 times with 3-ml. portions of concentrated sulphuric acid, and the pure hydrocarbon was isolated as usual after two distillations from sodium.

B. p. 203°/774 mm.; *M* 148·24; n_C 1·48478, n_D 1·48849, n_F 1·49802, $n_{G'}$ 1·50523; R_C 49·42, R_D 49·76, R_F 50·56, $R_{G'}$ 51·18; $Mn_D^{20°}$ 220·68. Densities determined: $d_{4°}^{20}$ 0·8594, $d_{4°}^{41·6°}$ 0·8440, $d_{4°}^{59·5°}$ 0·8306, $d_{4°}^{85·6°}$ 0·8091. Apparatus *D*.

t.	*H.*	$d_{4°}^{t°}$.	γ.	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	γ.	*P.*
18·4°	13·89	0·8606	29·52	401·5	61·3	12·50	0·8296	25·61	402·0
25·2	13·72	0·8556	28·99	402·0	87·4	11·62	0·8092	23·22	402·1
41·7	13·15	0·8439	27·41	401·9				Mean	401·9

Method 2. 70 G. of benzyl *n*-propyl ketone, b. p. 243—247°/757 mm. (XI, **134**), were reduced with 160 g. of amalgamated zinc and concentrated hydrochloric acid. Steam distillation afforded 64 g. of an organic liquid which, upon distillation from sodium, yielded 60 g. of crude *n*-amylbenzene, b. p. 197—205° (mainly 201—203°). This was washed 11 times with 10-ml. portions of concentrated sulphuric acid and yielded, after two distillations over sodium, as usual, 40 g. of the pure hydrocarbon.

B. p. 202·5°/774 mm.; *M* 148·24; n_C 1·48459, n_D 148835, n_F 1·49796, $n_{G'}$ 1·50552; R_C 49·40, R_D 49·73, R_F 50·56, $R_{G'}$ 51·21; $Mn_D^{20°}$ 220·64. Densities determined: $d_{4°}^{20°}$ 0·8593, $d_{4°}^{41·2°}$ 0·8438, $d_{4°}^{61·5°}$ 0·8286, $d_{4°}^{86·5°}$ 0·8098. Apparatus *D*.

13·2°	14·14	0·8643	30·18	402·0	41·1°	13·17	0·8439	27·45	402·1
19·9	13·88	0·8594	29·46	401·8	61·1	12·51	0·8289	25·61	402·3
24·4	13·74	0·8560	29·05	402·0	87·2	11·58	0·8093	23·15	401·8
								Mean	402·0

123. n-*Hexylbenzene.*—94 G. of 2-phenylethyl *n*-propyl ketone, b. p. 140—143°/17 mm. (XI, **137**), were reduced as in the last preparation. Steam distillation afforded 82 g. of an organic product which, when distilled over sodium, gave 54 g. of crude *n*-hexylbenzene, b. p. 218—230°, and 18 g. of a fraction, b. p. 230—240°, which was not investigated. The crude hydrocarbon was washed 15 times with 5-ml. portions of concentrated sulphuric acid and the pure *n*-hexylbenzene was isolated in the usual manner after two distillations over sodium.

B. p. 222·5°/766 mm.; *M* 162·26; n_C 1·48375, n_D 1·48739, n_F 1·49652, $n_{G'}$ 1·50399; R_C 53·95, R_D 54·29, R_F 55·15, $R_{G'}$ 55·86; $Mn_D^{20°}$ 241·35. Densities determined: $d_{4°}^{20°}$ 0·8602, $d_{4°}^{42·0°}$ 0·8441, $d_{4°}^{62·5°}$ 0·8292, $d_{4°}^{86·5°}$ 0·8116. Apparatus *A*.

19·8°	18·56	0·8603	29·90	441·0	60·5°	16·76	0·8309	26·08	441·3
24·1	18·37	0·8572	29·79	442·2	86·0	15·62	0·8120	23·75	441·1
40·1	17·74	0·8455	28·09	441·8				Mean	441·5

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128. *Physical Properties and Chemical Constitution. Part XI. Ketones.*

By ARTHUR I. VOGEL.

New experimental data for the parachors and refractivities of higher alkyl ketones and aryl alkyl ketones are presented. The CO contributions of aliphatic ketones have been calculated with the aid of the experimental data for aliphatic hydrocarbons (Part IX, *J.*, 1946, 133), and the following are regarded as the most probable values:

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
CO	45·9	4·684	4·713	4·768	4·830	42·38

These differ appreciably from the values previously accepted. The CO contributions for the aryl alkyl ketones have been computed by direct comparison with the experimental figures for *n*-alkylbenzenes (preceding paper).

EISENLOHR (*Z. physikal. Chem.*, 1910, **55**, 600) has computed the contribution of the carbonyl oxygen, O", to the molecular refractivity by subtracting nCH$_2$ from the molecular refractivities of 12 aldehydes and ketones $[CH_2]_nO$" and gives the following mean values [the figures for the CO contribution (= C + O") are also included for comparison with the author's results]:

	R_C.	R_D.	R_F.	$R_{G'}$.
O"	2·189	2·211	2·247	2·267
CO	4·602	2·629	4·685	4·733

Sugden, Reed, and Wilkins (*J.*, 1925, **127**, 1525; see also "The Parachor and Valency", 1930, **38**) state that a double bond gives an increment in parachor of about 23·2 in compounds

containing the links C=C, C=O, C=S, C=N, and N=O; the value for the parachor contribution of the carbonyl group is therefore C + O + ⊢ or 4·8 + 20·0 + 23·2 = 48·0. In Part V (*J.*, 1940, 171) experimental data were presented for the physical properties of a number of alkyl ketones which had been purified through the semicarbazones. The results of measurements upon further alkyl ketones and a number of aryl alkyl ketones are now given. To calculate the CO contribution, the author has subtracted the experimental figures for the corresponding hydrocarbon (Part IX, *J.*, 1946, 133) wherever this was possible [*e.g.*, $Bu^n_2CO - 2Bu^n$ ($\equiv n\text{-}C_8H_{18}$) = CO] or the calculated values for the alkyl groups. The figures for the alkyl groups employed in these calculations and also in succeeding papers of this series are collected in Table I; the values for higher alkyl groups (*n*-nonyl *et seq.*) may be obtained by subtracting

TABLE I.

Constants for alkyl groups.

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
CH_3	55·4	5·636	5·653	5·719	5·746	18·13
C_2H_5	95·4	10·260	10·300	10·414	10·481	38·72
$C_3H_7^n$	135·5	14·895	14·965	15·125	15·235	59·25
$C_3H_7^i$	133·8	14·905	14·975	15·145	15·255	58·95
$C_4H_9^n$	175·3	19·500	19·585	19·800	19·950	79·81
$C_4H_9^i$	173·8	19·530	19·620	19·840	19·990	79·54
$C_4H_9^s$	171·2	19·330	19·420	19·625	19·775	80·21
$C_5H_{11}^n$	215·0	24·140	24·250	24·515	24·700	100·46
$C_5H_{11}^i$ *	212·6	24·095	24·195	24·460	24·650	100·30
$C_5H_{11}^i$ †	213·1	24·170	24·280	24·540	24·720	100·21
$CHMePr^n$ (2-pentyl)	209·7	23·895	24·000	24·255	24·440	100·83
$CHEt_2$ (3-pentyl)	208·5	23·815	23·925	24·170	24·355	100·95
$C_6H_{13}^n$	255·0	28·725	28·855	29·160	29·385	121·10
$C_7H_{15}^n$	295·7	33·395	33·550	33·905	34·170	141·75
$C_8H_{17}^n$	335·7	37·960	38·135	38·535	38·830	162·43
C_3H_5 (allyl)	124·3	14·425	14·520	14·745	14·920	57·60

* From di*iso*amyl prepared from *iso*amyl bromide (*ex* Sharples synthetic *iso*amyl alcohol) and sodium.
† From di*iso*amyl prepared from *iso*amyl bromide (*ex* Bisol fermentation *iso*amyl alcohol) and sodium.

H from the *n*-alkyl hydrocarbons (Part IX, *loc. cit.*). The values for CH_3 were the mean figures deduced by subtracting $(n - 2)CH_2$ from the normal hydrocarbons C_nH_{2n+2}; C_2H_5 from $CH_3 + CH_2$; $C_3H_7^\beta$ from 0·5 (di*iso*butyl $- 2CH_2$); and C_3H_5 from diallyl.

The contributions of the CO group for the various alkyl ketones are collected in Table II. The lines marked with an asterisk are those for ketones which were regenerated from the semicarbazones (Part V, *J.*, 1940, 171); the other ketones were purified by fractionation only, and the data are therefore not quite so trustworthy. Two series of mean values are given:

TABLE II.

CO *Values for aliphatic ketones.*

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
Me_2CO *	50·9	4·77	4·80	4·86	4·94	42·74
$MeEtCO$ *	47·7	4·68	4·72	4·76	4·84	42·56
Et_2CO *	46·7	4·58	4·61	4·66	4·73	42·47
$MePr^nCO$ *	46·6	4·61	4·63	4·69	4·75	42·36
$EtPr^nCO$ *	45·5	4·65	4·68	4·73	4·78	42·32
$MeBu^nCO$ *	45·7	4·74	4·76	4·83	4·89	42·31
$MeBu^iCO$ *	46·8	4·84	4·88	4·93	4·99	42·11
Pr^n_2CO *	44·2	4·55	4·57	4·63	4·69	42·15
$EtBu^nCO$	44·9	4·55	4·56	4·62	4·67	42·37
$MeAm^nCO$ *	48·2	4·82	4·85	4·91	4·98	42·34
$EtAm^nCO$	42·7	4·48	4·49	4·55	4·58	42·43
$C_6H_{13}{}^nMeCO$ *	43·7	4·66	4·69	4·75	4·77	42·43
$C_6H_{13}{}^nEtCO$	44·8	4·55	4·57	4·63	4·67	42·61
Bu^n_2CO	43·5	4·56	4·59	4·64	4·68	42·29
Bu^i_2CO *	44·1	4·69	4·72	4·77	4·82	42·77
$MeC_7H_{15}{}^nCO$	43·9	4·74	4·77	4·82	4·88	42·50
$EtC_7H_{15}{}^nCO$	45·1	4·57	4·60	4·64	4·68	42·46
Am^n_2CO	42·5	4·61	4·62	4·67	4·72	42·23
$MeC_9H_{19}{}^nCO$	—	4·71	4·72	4·78	4·83	42·45
Mean (excluding Me_2CO)	45·1	4·644	4·668	4·723	4·772	42·39
Mean * (excluding Me_2CO)	45·9	4·684	4·713	4·768	4·830	42·38

the first (excluding acetone) includes all the ketones, and the second (which one would expect to be the more trustworthy) is deduced from the ketones *ex* semicarbazones. These results differ appreciably from those of Sugden (parachor) and Eisenlohr (refractivities). In view of the somewhat large individual variations from the mean, it is proposed to reinvestigate the whole subject later.

The results for a number of aryl alkyl ketones, which were purified by fractionation only, are collected in Table III; the values were obtained by subtraction of the experimental figures of the appropriate alkylbenzenes (preceding paper). It will be observed that the parachor contributions, except for the methyl ketones, approximate to those for the alkyl ketones, whilst the refractivities for those compounds in which the keto-group is directly attached to the aromatic ring appear to be uniformly high.

TABLE III.

CO *Values for aryl alkyl ketones.*

Ketone.	*P*.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
Ph·COMe	47·9	5·12	5·17	5·40	5·58	46·34
Ph·COEt	44·4	5·01	5·08	5·27	5·35	46·04
Ph·COPr^n	43·4	5·08	5·15	5·33	5·50	45·96
Ph·CH_2·COMe	48·6	4·70	4·73	4·80	[4·80]	44·64
Ph·CH_2·COEt	46·2	4·53	4·56	4·61	4·66	44·71
Ph·CH_2·COPr^n	44·3	4·50	4·54	4·61	4·66	44·42
Ph·CH_2·CH_2·COMe	49·8	4·60	4·64	4·68	4·73	44·85
Ph·CH_2·CH_2·COEt	47·4	4·47	4·50	4·56	4·59	44·77
Ph·CH_2·CH_2·COPr^n	44·5	4·45	4·47	4·52	4·58	44·14

EXPERIMENTAL.

Preparation of Ketones.—All the ketones, except those in which the CO group is directly attached to the benzene ring, were prepared by passing the appropriate acid or mixture of acids over thoria at 430—450°.

Preparation of thoria catalyst. 276 G. of commercially pure, finely-powdered thorium nitrate were dissolved in the minimum volume of water (*ca.* 450 ml.) and a solution of 106 g. of A.R. anhydrous sodium carbonate in 400 ml. of water was added slowly and with mechanical stirring. The heavy white precipitate was allowed to settle, as much as possible of the mother-liquor was decanted, and the precipitate washed once by decantation with 500 ml. of water. The resulting moist precipitate was made into a thick paste with distilled water, and pumice (4—8 mesh) was stirred in until most of the suspension appeared to be absorbed and the pumice was completely covered. The impregnated pumice was dried in *ca.* 200-g. lots by heating in a large evaporating dish upon an electric hot plate with constant stirring until the lumps no longer clung together. The cold product was sieved: about 250 g. of a white powder (largely thorium carbonate but containing some oxide) are recovered and can be used for impregnating more pumice. The total weight of impregnated pumice is about 1400 g.; the exact weight will, of course, depend upon the grade of the pumice.

The catalyst was packed into a hard-glass or Pyrex tube, 100 cm. long and 1·5 cm. in diameter. Small plugs of purified glass wool were inserted after each 15-cm. column of the catalyst; this device reduced the danger of carbonisation blocking the tube. The apparatus was set up as detailed in Part V (*J.*, 1940, 172) and the tube was heated to 430—450° in a slow stream of nitrogen; carbon dioxide (and generally oxides of nitrogen) were evolved. The decomposition of the thorium salt deposited upon the pumice was complete in 6—12 hours.

A temperature of 430—450° was employed in all the preparations.

Di-n-*butyl ketone.* 200 G. of *n*-valeric acid, b. p. 182·5—185·5°/750 mm. (Eastman Kodak), were circulated over the catalyst during 18 hours. The product was worked up as detailed in Part V (*loc. cit.*) and yielded, upon fractionation through a Pyrex Young and Thomas column, 50 g. of the crude ketone, b. p. 181—185°/756 mm. Upon refractionation, most boiled at 184°/750 mm., and a middle fraction was collected for the physical measurements. The poor yield of the ketone is probably due to the unsatisfactory character of the sample of the commercial acid used.

Di-n-*amyl ketone.* 200 G. of *n*-hexoic acid, b. p. 203—206° (Deutsche Hydrierwerke), were circulated over the catalyst during 22 hours; the distillate weighed 159 g., of which 15 g. constituted the aqueous layer. After removal of excess of acid and drying, distillation gave the following fractions: (1) 200—221°, 10 g.; (2) 221—225°, 100 g.; (3) 225—227°, 12 g.; and (4) 227—235°, 12 g. Upon redistillation of fraction (2), it boiled largely at 223°/760 mm. and a middle portion was taken for the physical measurements.

Ethyl n-*butyl ketone.* A mixture of 51 g. of *n*-valeric acid, b. p. 184—184·5°/768 mm. (*ex n*-butyl cyanide), and 111 g. of propionic acid, b. p. 139—141°/760 mm., was passed over the catalyst during 9 hours. The aqueous layer in the distillate was separated, and the organic layer washed successively with 10% sodium hydroxide solution and water and dried ($CaSO_4$). The mixture of ketones (74 g.) was distilled through a Widmer column and afforded 38 g. of diethyl ketone, b. p. 101—105°, 26 g. of ethyl *n*-butyl ketone, b. p. 145—146°/767 mm., and 8 g. of a high-b. p. residue composed largely of di-*n*-butyl ketone. Redistillation from a Claisen flask with fractionating side arm yielded the pure ethyl *n*-butyl ketone, b. p. 146·5°/765 mm.

Ethyl n-*amyl ketone.* A mixture of 77 g. of pure *n*-hexoic and 99 g. of pure propionic acid when circulated over thoria during 6 hours afforded 93 g. of the crude mixture of ketones. This was

separated by distillation into 32 g. of diethyl ketone, b. p. 101—104°, 40 g. of crude ethyl *n*-amyl ketone, b. p. 165—185°, and 14 g. of a high-b. p. residue (largely di-*n*-amyl ketone). The fraction, b. p. 165—185°, when distilled through a well-lagged, all-glass Dufton column, boiled largely at 166—168°, and a middle fraction, b. p. 167°/749 mm., was employed for the physical measurements.

Ethyl n-*hexyl ketone.* A mixture of 130 g. of *n*-heptoic acid, b. p. 216—218°/744 mm., and 148 g. of pure propionic acid was circulated over a thoria catalyst during 15 hours. The crude mixture of ketones (128 g.), isolated as detailed under ethyl *n*-butyl ketone, was distilled through a well-lagged, all-glass Dufton column and thus separated into 40 g. of diethyl ketone, b. p. 100—105°, 58 g. of ethyl *n*-hexyl ketone, b. p. 184—190° (largely 185—186°), and 27 g. of a dark residue composed largely of di-*n*-hexyl ketone. Upon redistillation of the ethyl *n*-hexyl ketone, it boiled largely at 187°/751 mm. and a middle fraction was used in the physical measurements.

Ethyl n-*heptyl ketone.* A mixture of 72 g. of *n*-octoic acid, b. p. 235—239°/762 mm. (Deutsche Hydrierwerke), and 111 g. of pure propionic acid was passed over the catalyst during 10 hours and afforded 98 g. of the crude mixture of ketones. A preliminary distillation gave 30 g. of diethyl ketone, b. p. 100—105°, 45 g. of crude ethyl *n*-heptyl ketone, b. p. 200—210°, and 6 g. of crude di-*n*-heptyl ketone. Redistillation of the main fraction through a well-lagged, all-glass Dufton column afforded pure ethyl *n*-heptyl ketone, b. p. 203°/754 mm.

Methyl n-*heptyl ketone.* A mixture of 96 g. of *n*-octoic acid (as above) and 320 g. of A.R. glacial acetic acid upon circulation over a thoria catalyst during 36 hours yielded, after thorough washing to remove acetone, 125 g. of the mixed ketones. The following fractions were collected upon distillation: (1) 180—190°, 7 g.; (2) 190—194°, 90 g.; (3) 194—206°, 15 g.; and (4) a high-b. p. residue (8 g.) which soldified on cooling. Fraction (4), after two crystallisations from dilute alcohol, gave 6 g. of pure di-*n*-heptyl ketone, m. p. 41°. Redistillation of fraction (2) yielded pure methyl *n*-heptyl ketone, b. p. 193°/749 mm.

Methyl n-*nonyl ketone.* A solution of 86 g. of decoic acid, m. p. 31—32° (Deutsche Hydrierwerke), in 120 g. of A.R. glacial acetic acid was circulated over the thoria catalyst during 16 hours. A small hot plate was placed immediately below the adaptor through which the mixture entered the catalyst tube in order to prevent solidification. It was necessary to warm the reaction product in order to keep it fluid while being worked up in the usual manner. Distillation of the resulting mixture of ketones (57 g.) through a well-lagged, all-glass Dufton column gave 7 g. of acetone, b. p. 56°, 40 g. of crude methyl *n*-nonyl ketone, b. p. 224—226°, and 6 g. of a high b. p. residue (largely di-*n*-nonyl ketone). Pure methyl *n*-nonyl ketone, b. p. 228·5°/748 mm., was obtained upon redistillation of the main fraction.

Benzyl methyl ketone. A solution of 170 g. of pure phenylacetic acid in 225 g. of A.R. glacial acetic acid was circulated over the catalyst during 18 hours: a slow stream of carbon dioxide was passed through the catalyst tube to keep the gases in motion. The distillate was worked up as detailed under ethyl *n*-butyl ketone except that the aqueous layer was extracted with two 50-ml. portions of benzene. After the removal of the solvent at atmospheric pressure, the mixture was distilled under reduced pressure and yielded 88 g. of benzyl methyl ketone, b. p. 100—102·5°/20 mm. (mainly 102—102·5°/20 mm.) (compare *Org. Synth.*, 1936, **16**, 47, in which different proportions of the acids are employed and the b. p. of the crude ketone is given as 110—120°/21—22 mm.), and a residue (16 g.) of crude dibenzyl ketone. Redistillation gave the pure benzyl methyl ketone, b. p. 102·5°/19 mm.

Benzyl ethyl ketone. A mixture of 204 g. of pure phenylacetic acid and 333 g. of pure propionic acid was circulated over the catalyst during 16 hours. The distillate was worked up as for benzyl methyl ketone except that the extraction with benzene was omitted. The dry, crude mixture of ketones (320 g.) was distilled through a three-section Pyrex Young and Thomas column to separate the diethyl ketone, b. p. 99—103° (165 g.). The residue was distilled under reduced pressure and gave 110 g. of crude benzyl ethyl ketone, b. p. 118—123°/22 mm., and a residue (34 g.) of impure dibenzyl ketone. Upon redistillation the main fraction boiled at 113—115°/17 mm., from which a middle fraction, b. p. 113·5°/17 mm., was removed for the physical measurements.

Benzyl n-*propyl ketone.* A solution of 204 g. of pure phenylacetic acid in 396 g. of *n*-butyric acid, b. p. 162—163°/765 mm., was circulated over a thoria catalyst during 20 hours. The distillate yielded 368 g. of the dry, crude mixture of ketones, which was separated, as for ethyl benzyl ketone, into 185 g. of di-*n*-propyl ketone, b. p. 140—145°, 108 g. of crude benzyl *n*-propyl ketone, b. p. 240—260°, and 49 g. of impure dibenzyl ketone. Redistillation of the main fraction yielded the pure ketone, b. p. 243—247°/757 mm., from which a middle fraction, b. p. 244°/757 mm., was employed in the physical measurements.

Methyl 2-phenylethyl ketone. A solution of 100 g. of β-phenylpropionic acid, m. p. 48°, in 160 g. of A.R. glacial acetic acid was slowly circulated over a thoria catalyst. The dry, crude mixture of ketones (88 g.) upon distillation yielded 70 g. of crude methyl 2-phenylethyl ketone, b. p. 230—235°. The pure ketone, b. p. 234·5°/770 mm., was obtained upon redistillation.

Ethyl 2-phenylethyl ketone. A solution of 100 g. of pure β-phenylpropionic acid in 200 g. of pure propionic acid was circulated over a thoria catalyst during 11 hours. The distillate yielded 171 g. of the crude, dry mixed ketones. This was worked up as for benzyl ethyl ketone and afforded 75 g. of diethyl ketone, b. p. 100—103°, 72 g. of crude ethyl 2-phenylethyl ketone, b. p. 245—249°, and 15 g. of impure di-2-phenylethyl ketone. The main fraction gave the pure ketone, b. p. 248°/763 mm., upon redistillation.

2-Phenylethyl n-*propyl ketone.* A solution of 200 g. of pure β-phenylpropionic acid in 469 g. of pure *n*-butyric acid was circulated over a thoria catalyst during 15 hours. The distillate yielded 338 g. of crude, dry mixed ketones. This was worked up as for benzyl ethyl ketone and gave 194 g. of di-*n*-propyl ketone, b. p. 140—144°, 130 g. of 2-phenylethyl *n*-propyl ketone, b. p. 139—143°/17 mm., and 44 g. of impure di-2-phenylethyl ketone. Redistillation yielded the pure ketone, b. p. 138·5°/16 mm.

Acetophenone. A pure commercial sample was distilled and a middle fraction, b. p. 200°/759 mm., collected.

Propiophenone. 238 G. of redistilled thionyl chloride were placed in a 500-ml. Claisen flask with fractionating side arm; this was fitted with a dropping-funnel in the long neck, a reflux condenser

(attached to a gas absorption device) in the short neck, and a small cork in the side arm. The flask was heated on a water-bath, 148 g. of pure propionic acid were added during 2 hours, and the mixture was then refluxed for 30 minutes, and fractionally distilled. The yield of propionyl chloride, b. p. 78—81°/777 mm., was 100 g.

A mixture of 234 g. of sodium-dried A. R. benzene and 135·5 g. of anhydrous aluminium chloride was placed in a 1·5-l. three-necked flask provided with a dropping-funnel, a mercury-sealed mechanical stirrer, and an efficient reflux condenser. The dropping-funnel was charged with 90 g. of propionyl chloride and about 2—3 ml. were added to the stirred mixture. Evolution of hydrogen chloride commenced after 1—2 minutes' warming, the flame was removed, and the chloride added dropwise during 2—3 hours, after which the reaction mixture was refluxed for 0·5 hour, allowed to cool, and added to 1 l. of water, which was vigorously stirred in a 3 l. beaker; the temperature was kept below 10° by addition of ice. The benzene layer was separated, washed twice with 10% sodium hydroxide solution, then with water and dried ($MgSO_4$). The benzene was removed and the residue distilled; 78 g. of propiophenone, b. p. 214·5—216·5°/763 mm., were obtained. Redistillation gave pure propiophenone, b. p. 215°/763 mm.

Butyrophenone. The reaction between 134 g. of anhydrous aluminium chloride, 234 g. of sodium-dried A.R. benzene, and 105 g. of *n*-butyryl chloride, b. p. 100·5—102·5°/777 mm., as detailed under propiophenone, yielded 90 g. of butyrophenone, b. p. 227—229°/777 m. Redistillation gave the pure compound, b. p. 228°/777 mm.

124. *Di*-n-*butyl ketone.* B. p. 184°/750 mm.; M 142·23; n_C 1·41730, n_D 1·41946, n_F 1·42467, $n_{G'}$ 1·42852; R_C 43·56, R_D 43·76, R_F 44·22, $R_{G'}$ 44·58; $Mn_D^{20°}$ 201·90. Densities determined: $d_4^{20°}$ 0·8217, $d_4^{40·7°}$ 0·8056, $d_4^{60·6°}$ 0·7895, $d_4^{86·6°}$ 0·7700. Apparatus *D*.

(These headings apply to corresponding columns in all the following tables.)

t.	H.	$d_4^{t°}$.	γ.	P.	t.	H.	$d_4^{t°}$.	γ.	P.
21·1°	13·12	0·8208	26·60	393·5	62·6°	11·73	0·7879	22·82	394·5
26·9	12·95	0·8163	26·11	393·8	87·4	10·91	0·7694	20·73	394·4
41·1	12·41	0·8053	24·68	393·7				Mean	394·0

125. *Di*-n-*amyl ketone.* B. p. 223°/760·5 mm.; M 170·19; n_C 1·42571, n_D 1·42782, n_F 1·43321, $n_{G'}$ 1·43711; R_C 52·89, R_D 53·12, R_F 53·70, $R_{G'}$ 54·12; $Mn_D^{20°}$ 243·14. Densities determined: $d_4^{20°}$ 0·8245, $d_4^{41·5°}$ 0·8097, $d_4^{60·5°}$ 0·7956, $d_4^{86·0°}$ 0·7762. Apparatus *A*.

19·4°	17·74	0·8249	27·40	472·3	62·4°	15·81	0·7943	23·51	472·1
41·8	16·76	0·8095	25·40	472·3	87·7	14·77	0·7750	21·43	472·8
								Mean	472·4

126. *Ethyl* n-*butyl ketone.* B. p. 146·5—147°/765 mm.; M 114·18; n_C 1·40671, n_D 1·40880, n_F 1·41390, $n_{G'}$ 1·41759; R_C 34·34, R_D 34·49, R_F 34·87, $R_{G'}$ 35·14; $Mn_D^{20°}$ 160·86. Densities determined: $d_4^{20°}$ 0·8181, $d_4^{40·5°}$ 0·8008, $d_4^{61·9°}$ 0·7829, $d_4^{86·5°}$ 0·7611. Apparatus *A*.

16·1°	17·26	0·8214	26·55	315·5	61·6°	15·09	0·7832	22·13	316·2
20·0	17·17	0·8181	26·30	316·1	87·2	13·73	0·7605	19·55	315·7
40·9	16·00	0·8005	23·98	315·4				Mean	315·8

127. *Ethyl* n-*amyl ketone.* B. p. 167°/749 mm.; M 128·21; n_C 1·41328, n_D 1·41541, n_F 1·42060, $n_{G'}$ 1·42431; R_C 38·92, R_D 39·09, R_F 39·52, $R_{G'}$ 39·82; $Mn_D^{20°}$ 181·47. Densities determined: $d_4^{20°}$ 0·8220, $d_4^{41·2°}$ 0·8054, $d_4^{61·0°}$ 0·7903, $d_4^{86·1°}$ 0·7693. Apparatus *A*.

14·5°	17·58	0·8263	27·20	354·3	40·9°	16·36	0·8056	24·68	354·7
19·7	17·42	0·8223	26·82	354·8	61·0	15·47	0·7903	22·89	354·9
22·9	17·21	0·8197	26·42	354·6	87·1	14·21	0·7685	20·45	354·8
								Mean	354·7

128. *Ethyl* n-*hexyl ketone.* B. p. 187°/751 mm.; M 142·23; n_C 1·41861, n_D 1·42081, n_F 1·42608, $n_{G'}$ 1·42990; R_C 43·55; R_D 43·74, R_F 44·23, $R_{G'}$ 44·57; $Mn_D^{20°}$ 202·22. Densities determined: $d_4^{20°}$ 0·8241, $d_4^{40·7°}$ 0·8014, $d_4^{60·1°}$ 0·7921, $d_4^{84·9°}$ 0·7725. Apparatus *A*.

17·3°	17·92	0·8263	27·73	395·0	60·7°	15·82	0·7916	23·45	395·4
20·4	17·76	0·8238	27·40	395·0	87·2	14·65	0·7707	21·14	395·7
40·0	16·86	0·8080	25·50	395·6				Mean	395·3

129. *Ethyl* n-*heptyl ketone.* B. p. 203°/754 mm.; M 156·26; n_C 1·42302, n_D 1·42521, n_F 1·43052, $n_{G'}$ 1·43447; R_C 48·23, R_D 48·45, R_F 48·97, $R_{G'}$ 49·37; $Mn_D^{20°}$ 222·70. Densities determined: $d_4^{20°}$ 0·8251, $d_4^{39·6°}$ 0·8109, $d_4^{60·6°}$ 0·7951, $d_4^{85·7°}$ 0·7761. Apparatus *A*.

21·2°	18·02	0·8242	27·68	435·4	61·3°	16·24	0·7946	24·16	436·0
40·9	17·15	0·8099	26·01	435·7	86·1	15·11	0·7758	21·95	436·0
								Mean	435·8

130. *Methyl* n-*heptyl ketone.* B. p. 193°/749 mm.; M 142·23; n_C 1·41878, n_D 1·42096, n_F 1·42625, $n_{G'}$ 1·43021; R_C 43·74, R_D 43·94, R_F 44·42, $R_{G'}$ 44·78; $Mn_D^{20°}$ 202·11. Densities determined: $d_4^{20°}$ 0·8208, $d_4^{40·5°}$ 0·8059, $d_4^{60·7°}$ 0·7901, $d_4^{85·5°}$ 0·7705. Apparatus *A*.

20·3°	17·14	0·8206	26·34	392·7	61·5°	15·49	0·7985	22·90	394·1
41·0	16·50	0·8055	24·89	394·4	88·2	14·62	0·7685	21·04	396·4
								Mean	394·4

131. *Methyl* n-*nonyl ketone.* B. p. 228·5°/748 mm.; M 170·29; n_C 1·42686, n_D 1·42907, n_F 1·43448, $n_{G'}$ 1·43843; R_C 52·99, R_D 53·22, R_F 53·81, $R_{G'}$ 54·23; $Mn_D^{20°}$ 243·36. Densities determined: $d_4^{20°}$ 0·8250, $d_4^{41·6}$ 0·8098, $d_4^{60·6°}$ 0·7955, $d_4^{85·8°}$ 0·7770. The results of the surface tension measurements were unsatisfactory (P = 470—480) and the meniscus was not always clear; presumably the contact angle is not zero and determinations should be made by the maximum bubble-pressure method.

132. *Benzyl methyl ketone.* B. p. 102·5°/19 mm.; M 134·17; n_C 1·51195, n_D 1·51635, n_F 1·52756, $n_{G'}$ 1·5370 (approximate; line difficult to see); R_C 40·19, R_D 40·48, R_F 41·21, $R_{G'}$ 41·83; $Mn_D^{20°}$ 203·46. Densities determined: $d_4^{20°}$ 1·0018, $d_4^{40·3°}$ 0·9850, $d_4^{59·9°}$ 0·9690, $d_4^{85·3°}$ 0·9470. Apparatus *A*.

t.	H.	$d_{4°}^{t°}$.	γ.	P.	t.	H.	$d_{4°}^{t°}$.	γ.	P.
19·2°	20·28	1·0025	38·07	332·4	60·7°	18·40	0·9683	33·36	333·0
23·1	20·15	0·9992	37·70	332·7	86·0	17·26	0·9464	30·59	333·4
40·2	19·37	0·9851	35·73	333·0				Mean	332·9

133. *Benzyl ethyl ketone.* B. p. 113·5°/17 mm.; M 148·20; n_C 1·50728, n_D 1·51146, n_F 1·52205, $n_{G'}$ 1·53061; R_C 44·68, R_D 44·99, R_F 45·77, $R_{G'}$ 46·39; $Mn_D^{20°}$ 224·00. Densities determined: $d_4^{20°}$ 0·9877, $d_4^{40·4°}$ 0·9717, $d_4^{60·8°}$ 0·9556, $d_4^{85·9°}$ 0·9344. Apparatus *A*.

19·7°	19·82	0·9879	36·66	369·1	61·2°	18·03	0·9553	32·25	369·7
20·3	19·74	0·9875	36·50	368·9	87·3	16·87	0·9333	29·48	370·0
41·2	18·87	0·9711	34·31	369·4				Mean	369·4

134. *'Benzyl* n-*propyl ketone.* B. p. 243·5—244°/757 mm.; M 162·21; n_C 1·50227, n_D 1·50627, n_F 1·51649, $n_{G'}$ 1·52465; R_C 49·28, R_D 49·62, R_F 50·46, $R_{G'}$ 51·13; $Mn_D^{20°}$ 244·34. Densities determined: $d_4^{20°}$ 0·9718, $d_4^{40·2°}$ 0·9550, $d_4^{61·4°}$ 0·9386, $d_4^{85·9°}$ 0·9188. Apparatus *A*.

20·0°	19·21	0·9718	34·96	405·6	60·9°	17·45	0·9390	30·68	406·6
21·3	19·14	0·9708	34·79	405·8	86·9	16·43	0·9180	28·24	407·3
40·5	18·36	0·9548	32·83	406·6				Mean	406·3

135. *Methyl* 2-*phenylethyl ketone* (*benzylacetone*). B. p. 234·5°/770 mm.; M 148·20; n_C 1·50824, n_D 1·51237, n_F 1·52285, $n_{G'}$ 1·53130; R_C 44·75, R_D 45·07, R_F 45·84, $R_{G'}$ 46·46; $Mn_D^{20°}$ 224·14. Densities determined: $d_4^{20°}$ 0·9875, $d_4^{41·1°}$ 0·9711, $d_4^{60·8°}$ 0·9562, $d_4^{86·9°}$ 0·9348. Apparatus *D*.

19·0°	15·60	0·9867	38·01	372·9	62·0°	14·17	0·9533	33·43	373·0
26·8	15·37	0·9822	37·28	372·8	86·7	13·36	0·9350	30·85	373·5
41·3	14·85	0·9709	35·61	372·9				Mean	373·0

136. *Ethyl* 2-*phenylethyl ketone.* B. p. 247·5—248·5°/763 mm.; M 162·22; n_C 1·50451, n_D 1·50851, n_F 1·51864, $n_{G'}$ 1·52664; R_C 49·25, R_D 49·58; R_F 50·41, $R_{G'}$ 51·06; $Mn_D^{20°}$ 244·69. Densities determined: $d_4^{20°}$ 0·9760, $d_4^{41·0°}$ 0·9597, $d_4^{60·8°}$ 0·9439, $d_4^{86·7°}$ 0·9240. Apparatus *A*.

18·7°	20·00	0·9770	36·59	408·4	61·2°	18·30	0·9436	32·33	410·0
28·5	19·74	0·9694	35·83	409·4	85·8	17·25	0·9247	29·87	410·1
40·7	19·11	0·9599	34·35	409·1				Mean	409·4

137. 2-*Phenylethyl* n-*propyl ketone.* B. p. 138·5°/16 mm.; M 176·25; n_C 1·49852, n_D 1·50232, n_F 1·51196, $n_{G'}$ 1·51976; R_C 53·85, R_D 54·20, R_F 55·08, $R_{G'}$ 55·79; $Mn_D^{20°}$ 264·78. Densities determined: $d_4^{20°}$ 0·9602, $d_4^{40·9°}$ 0·9445, $d_4^{59·0°}$ 0·9310, $d_4^{85·9°}$ 0·9100. Apparatus *A*.

19·7°	19·43	0·9604	34·94	446·2	59·9°	17·75	0·9303	30·92	446·8
23·2	19·28	0·9577	34·57	446·3	85·0	16·75	0·9107	28·56	447·3
40·5	18·46	0·9448	32·66	446·0				Mean	446·5

138. *Acetophenone.* B. p. 200°/759 mm.; M 120·14; n_C 1·52803, n_D 1·53349, n_F 1·54782, $n_{G'}$ 1·55982; R_C 35·98, R_D 36·27, R_F 37·10, $R_{G'}$ 37·77; $Mn_D^{20°}$ 184·23. Densities determined: $d_4^{20°}$ 1·0282, $d_4^{41·2°}$ 1·0113, $d_4^{60·8°}$ 0·9949, $d_4^{85·7°}$ 0·9739. Apparatus *A*.

17·8°	20·69	1·0300	39·90	293·2	61·0°	18·67	0·9947	34·77	293·3
25·1	20·35	1·0240	39·02	293·2	86·2	17·58	0·9734	32·04	293·6
40·0	19·69	1·0119	37·31	293·4				Mean	293·3

139. *Propiophenone.* B. p. 215°/763 mm.; M 134·17; n_C 1·52181, n_D 1·52688, n_F 1·54008, $n_{G'}$ 1·55106; R_C 40·50, R_D 40·83, R_F 41·68, $R_{G'}$ 42·38; $Mn_D^{20°}$ 204·86. Densities determined: $d_4^{20°}$ 1·0101, $d_4^{41·8°}$ 0·9934, $d_4^{61·2°}$ 0·9776, $d_4^{85·8°}$ 0·9572. Apparatus *D*.

22·3°	14·95	1·0082	37·22	328·7	60·1°	13·69	0·9785	33·08	328·8
24·5	14·80	1·0065	36·79	328·3	86·7	12·80	0·9562	30·23	329·0
41·4	14·29	0·9937	35·07	328·7				Mean	328·7

140. *Butyrophenone.* B. p. 228°/777 mm.; M 148·20; n_C 1·51511, n_D 1·51988, n_F 1·53234, n_G 1·54248; R_C 45·23, R_D 45·58, R_F 46·49, $R_{G'}$ 47·23; $Mn_D^{20°}$ 225·25. Densities determined: $d_4^{20°}$ 0·9885, $d_4^{41·5°}$ 0·9727, $d_4^{61·0°}$ 0·9575, $d_4^{86·0°}$ 0·9370. Apparatus *D*.

24·5°	14·41	0·9851	35·06	366·1	61·4°	13·30	0·9572	31·44	366·6
29·3	14·34	0·9814	34·76	366·7	86·9	12·61	0·9363	29·16	367·8
41·0	13·87	0·9731	33·33	365·9				Mean	366·6

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129. *Physical Properties and Chemical Constitution. Part XII. Ethers and Acetals.*

By Arthur I. Vogel

New measurements of the parachors and refractivities of a considerable number of aliphatic ethers and acetals have been made and the contributions of the O atom have been computed with the aid of the experimental data (or figures deduced therefrom) on the hydrocarbons (Part IX, *J.*, 1943, 133). The mean results are :

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
O (in ethers)	19·8	1·753	1·764	1·786	1·805	22·74
O (in acetals)	18·0	1·603	1·607	1·618	1·627	22·41

Similar measurements and calculations have been made on a number of phenyl alkyl ethers.

The parachor of oxygen is given by Sugden (*J.*, 1924, **125**, 1177; " The Parachor and Valency," 1930, 38) as 20·0 but no indication of the data from which this figure was calculated is disclosed. Eisenlohr (*Z. physikal. Chem.*, 1910, **75**, 607) deduced " Athersauerstoff " O< : (*a*) by subtracting the computed refractivities of $[CH_2]_n + O''$ (ketones) from the observed refractivities of esters $[CH_2]_nO''O<$ (16 esters), and (*b*) by subtracting the computed refractivities of $[CH_2]_n + H_2$ from the observed refractivities of ethers $[CH_2]_nH_2O<$ (4 ethers comprising ethyl propyl ether, methylal, acetal, and paraldehyde).

Wide individual variations were found (and indeed might have been anticipated from the procedure employed), and the mean values were given as :

	R_C.	R_D.	R_F.	$R_{G'}$.
O<	1·639	1·643	1·649	1·662
O·	1·522	1·525	1·531	1·541

The figures for " Hydroxylsauerstoff " O·, deduced by subtraction of the computed refractivities of $[CH_2]_n + O''$ from the observed refractivities of the acids $[CH_2]_nO''O·$ (8 monocarboxylic acids), are given above for purposes of comparison.

The author computes the parachor and refractivities of the oxygen atom in aliphatic ethers by simple subtraction of his own results for the appropriate hydrocarbon (Part IX, *J.*, 1946, 133) from those of the ethers; for diethyl and di*iso*propyl ether, the values for the alkyl groups (preceding paper) have been employed, whilst for 2 : 2′-dichlorodiethyl ether the figures for $Cl·CH_2·CH_2·CH_2Cl$ (XIV, **282**) + CH_2 were subtracted. The results for aliphatic ethers are collected in Table I.

Table I.

O *Values for aliphatic ethers.*

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
Et_2O	21·2	1·88	1·91	1·93	1·96	22·82
Pr^n_2O	19·5	1·72	1·75	1·77	1·80	22·60
Pr^i_2O *	21·7	1·76	1·76	1·76	1·78	21·90
Bu^n_2O	19·9	1·69	1·72	1·73	1·75	22·57
Am^n_2O	20·5	1·66	1·67	1·68	1·70	22·57
Am^i_2O †	20·1	1·71	1·72	1·74	1·76	22·43
Am^i_2O ‡	20·6	1·85	1·88	1·90	1·91	22·34
$(C_6H_{13}{}^n)_2O$	19·9	1·77	1·77	1·80	1·82	22·47
$(C_7H_{15}{}^n)_2O$	19·3	1·71	1·71	1·74	1·75	22·53
$(C_8H_{15}{}^n)_2O$	19·8	1·83	1·83	1·86	1·90	22·48
$MeBu^nO$	19·0	1·74	1·74	1·77	1·79	23·10
$EtBu^nO$	19·6	1·79	1·80	1·83	1·84	22·69
$MeAm^nO$	19·7	1·71	1·72	1·74	1·77	23·25
$EtAm^nO$	18·5	1·76	1·76	1·78	1·80	22·79
$MeC_6H_{13}{}^nO$	18·2	1·66	1·66	1·68	1·69	23·31
$EtC_6H_{13}{}^nO$	19·3	1·77	1·78	1·81	1·83	22·80
$(Cl·CH_2·CH_2)_2O$	21·8	1·79	1·79	1·81	1·81	23·16
Mean (excluding *)	19·8	1·753	1·764	1·786	1·805	22·74
$(CH_2·CH_2·OEt)_2O$	19·6	1·76	1·77	1·79	1·80	23·12
$(MeO·CH_2·CH_2·O·CH_2·CH_2)_2O$	20·5	1·73	1·74	1·75	1·77	23·50

† From Bisol fermentation *iso*amyl alcohol. ‡ From Sharples synthetic *iso*amyl alcohol.

Attention is drawn to the results for diethyleneglycol diethyl ether (" diethyl carbitol ") and tetramethyleneglycol dimethyl ether (" dimethoxy tetraglycol ") which, although containing

three and five oxygen atoms respectively, give results in reasonable agreement with those for the simple dialkyl ethers.

The results for phenyl alkyl ethers are collected in Table II; the experimental figures for the *n*-alkylbenzenes (Part X, this vol., p. 607) were employed in the calculations. It will be noted that the parachor values are of the same order as those for alkyl ethers, but the refractivities are consistently higher.

TABLE II.

O *Values for phenyl alkyl ethers.*

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
PhOMe	20·0	1·77	1·78	1·85	1·90	26·23
PhOEt	19·4	1·93	1·95	2·03	[2·01]	25·32
PhOPr^n	18·6	1·83	1·85	1·91	1·97	24·97
PhOPr^i	20·8	1·98	2·00	2·08	2·14	24·76
PhOBu^n	19·7	1·95	1·98	2·05	2·10	24·96
PhOAm^n	19·5	1·88	1·91	1·96	1·99	24·85
PhOC$_6$H$_{13}^n$	18·8	2·05	2·09	2·17	2·20	24·64

The results for acetals, collected in Table III, were entirely unexpected. The parachor and refractivities of the oxygen atom in acetals are consistently smaller than for the oxygen atom in alkyl ethers.

TABLE III.

2O *Values for acetals.*

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
$CH_2(OMe)_2$ *	39·6	3·23	3·25	3·27	3·31	44·30
$CH_2(OEt)_2$	37·1	3·24	3·25	3·28	3·31	44·98
$CH_2(OPr^n)_2$	36·4	3·20	3·20	3·23	3·24	45·03
$CH_2(OPr^i)_2$ *	38·7	3·20	3·19	3·20	3·22	44·68
$CH_2(OBu^n)_2$	36·6	3·23	3·24	3·26	3·26	45·03
$CH_2(OBu^i)_2$	36·6	3·26	3·26	3·28	3·30	44·74
$CH_2(OAm^n)_2$	35·8	3·21	3·23	3·25	3·27	45·18
$CH_2(OC_6H_{13}^n)_2$	36·9	3·12	3·14	3·16	3·18	45·18
$CH_3{\cdot}CH(OMe)_2$ *	38·3	3·11	3·13	3·15	3·18	45·71
$CH_3{\cdot}CH(OEt)_2$	36·3	3·23	3·23	3·26	3·29	44·64
$CH_3{\cdot}CH(OPr^n)_2$	35·5	3·19	3·20	3·21	3·23	44·62
$CH_3{\cdot}CH(OBu^n)_2$	34·9	3·17	3·18	3·18	3·22	44·56
$CH_3{\cdot}CH(OBu^i)_2$	34·2	3·21	3·21	3·24	3·24	44·20
Mean 2O (excluding *)	36·0	3·206	3·214	3·235	3·254	44·82
Mean O	18·0	1·603	1·607	1·618	1·627	22·41

EXPERIMENTAL.

Preparation of Symmetrical Ethers.—Diethyl ether was prepared in the usual manner from absolute ethyl alcohol and concentrated sulphuric acid, dried over anhydrous calcium chloride for 24 hours, and fractionated from sodium.

The first preparations of di-*n*-propyl, di-*n*-butyl, and di-*n*-amyl ethers were carried out by Popelier's method (*Bull. Soc. chim. Belg.*, 1923, **32**, 179); for the first two the excess of alcohol was removed by repeated washing with water; for the third the excess of amyl alcohol was removed by two washings with 50% (by vol.) sulphuric acid. In all cases the ether was finally refluxed and distilled from sodium to constant density and refractive index. When the physical measurements for these compounds had been completed, a new procedure was discovered for the preparation of di-*n*-butyl and higher ethers: this involved heating the alcohol with concentrated sulphuric acid until the theoretical volume of water was collected. The apparatus consisted of a bolt-head flask fitted with a cork carrying a thermometer (dipping almost to the bottom of the flask) and an uncalibrated Dean and Stark tube ("water separator" tube) attached to a short reflux condenser; the "water separator" tube permits of the automatic separation of the water produced in the reaction. The volume, v, of the "water separator" tube to the overflow point is first determined by adding water from a burette; the theoretical volume, v_t, of water eliminated in the formation of the ether from the alcohol is then calculated and the "water separator" tube is then charged with $(v - v_t)$ ml. of water. The apparatus is then completely assembled with the alcohol and the concentrated sulphuric acid in the bolt-head flask. The flask is then heated so that the mixture refluxes gently: the heating is stopped when the theoretical volume of water (within 10%) has been collected. In practice, it is found that the completion of the reaction usually corresponds to a definite temperature of the reaction mixture and the odour of sulphur dioxide then becomes apparent; further heating results in charring and formation of unsaturated hydrocarbons. To isolate the ether, the reaction product is distilled in steam, and the organic layer removed, dried, and fractionally distilled. The main fraction is then refluxed and distilled from sodium until the latter remains unattacked. The yield of ether may be improved by refluxing the fraction of low b. p., which contains a larger proportion of unchanged alcohol, repeatedly with sodium. For di-*n*-butyl ether the *n*-butyl alcohol may be removed more simply by washing with 50% (by weight) sulphuric acid. Some typical results are

collected below. It is not advisable to raise the temperature in the *n*-octyl ether preparation above 190°, since considerable carbonisation may occur.

Ether.	Wt. of alcohol, g.	Wt. of H_2SO_4, g.	Temp. for completion of reaction.	Yield of pure ether, g.
Di-*n*-butyl	50	16	134°	15
Di-*n*-amyl	50	7	157	23
Di*iso*amyl	50	7	148	24
Di-*n*-hexyl	50	6	180	20
Di-*n*-heptyl	40	4·2	198	17
Di-*n*-octyl	27	4·9	190	13

Commercial di*iso*propyl ether was shaken successively with a concentrated solution of a ferrous salt (to remove peroxides), 0·5% potassium permanganate solution (to remove traces of aldehydes), 5% sodium hydroxide solution, and water. It was then dried ($MgSO_4$), refluxed over sodium, and distilled from fresh sodium until the latter was unattacked. 2 : 2′-Dichlorodiethyl ether (Carbon and Carbide Corporation) was similarly purified.

Preparation of Unsymmetrical Ethers.—Two difficulties arise in the preparation of higher mixed aliphatic ethers by Williamson's method: (i) the slow reaction between 1 atom of sodium and 1—2 mols. of the alcohol to give the sodium alkoxide in view of the slight solubility of the alkoxide in the alcohol, and (ii) the difficulty of removing a large proportion of alcohol from the resulting ether by refluxing with sodium. These were overcome by employing 1 atom of sodium to 8—10 mols. of the alcohol, adding 1 mol. of the alkyl bromide or iodide (*i.e.*, equivalent to the sodium used), refluxing for 1—2 hours until formation of the ether was complete, and then removing the ether formed by fractional distillation; the process could, in general, be repeated 3 times and a reasonable yield of ether was obtained. The residual alcohol may also be recovered.

Ethyl n-*butyl ether*. The apparatus consisted of a 350-ml. Claisen flask with fractionating side arm; the short neck carried a double-surface condenser in the top of which a separatory funnel was supported by means of a grooved cork: the other neck and side arm were closed by means of well-fitting corks. 148 G. of *n*-butyl alcohol (b. p. 116—117°/750 mm.) were placed in the flask, 5·75 g. of clean sodium were added, and the mixture was warmed in an air-bath until all the sodium had reacted. 39 G. of pure ethyl iodide were then added, but there was no apparent reaction in the cold; upon gentle warming, sodium iodide gradually separated and the reaction appeared complete after 90 minutes. The condenser was removed and the apparatus was arranged for distillation: the crude ether (28 g.) was collected at 94—105°. After cooling, the flask was fitted with a double-surface condenser, etc., as before, 5·75 g. of sodium were added and the flask was warmed until reaction was complete; 39 g. of ethyl iodide were then introduced, the mixture was refluxed as before and then distilled, the fraction (40 g.) boiling up to 109° (largely at 100—103°) being collected. The combined distillates were refluxed for 2 hours with excess of sodium and distilled; the distillate was distilled from fresh sodium and passed over at 101—102°. After two further distillations from sodium, the latter remained unaffected and pure ethyl *n*-butyl ether, b. p. 91·5°/757 mm., was obtained. The yield was 36 g.

Methyl n-*butyl ether*. The quantities employed were: 148 g. of *n*-butyl alcohol, 5·75 g. of sodium, and 36 g. of pure methyl iodide; this yielded 27 g. of the crude ether, b. p. 65—85°. Repetition with a further 5·75 g. of sodium and 36 g. of methyl iodide afforded 28 g. of crude ether, b. p. 65—91°. The pure methyl *n*-butyl ether, b. p. 70·5°/766 mm. (31 g.), was obtained after repeated distillation from sodium.

Methyl n-*amyl ether*. 176 G. of *n*-amyl alcohol, b. p. 136·5—137·5°/766 mm. (Kodak), 5·75 g. of sodium (the reaction was allowed to proceed overnight), and 39 g. of ethyl iodide gave 25 g. of the crude ether, b. p. 95—110°; another reaction with the same quantities of sodium and methyl iodide afforded 35 g. of the crude ether, b. p. 100—108°. The yield of pure methyl *n*-amyl ether, b. p. 99°/763 mm., was 43 g.

Ethyl n-*amyl ether*. 5·75 G. of sodium were allowed to react overnight with 220 g. of *n*-amyl alcohol, 39 g. of ethyl iodide added, the mixture was refluxed for 3 hours, and the crude ether, b. p. 110—125° (35 g.), separated by distillation. Treatment of the residual alcohol with 5·75 g. of sodium, followed by 39 g. of ethyl iodide, afforded a further 41 g. of the crude ether, b. p. 120—129°. Repeated distillation over sodium gave 27 g. of pure ethyl *n*-amyl ether, b. p. 117·5—118·5°/768 mm.

Methyl n-*hexyl ether*. 192 G. of *n*-hexyl alcohol, b. p. 156—157°/765 mm., 5·41 g. of sodium and 33·5 g. of methyl iodide yielded, as for ethyl *n*-butyl ether, 27 g. of the crude ether, b. p. 130—140°. Addition of 5·41 g. of sodium to the residue, followed, after 12 hours, by 33·5 g. of methyl iodide gave a further 35 g. of the crude ether, b. p. 130—140°. Three distillations from excess of sodium afforded 42 g. of pure methyl *n*-hexyl ether, b. p. 126°/770 mm.

Ethyl n-*hexyl ether*. 204 G. of *n*-hexyl alcohol, 5·75 g. of sodium, and 39 g. of ethyl iodide gave 27 g. of the crude ether, b. p. 143—150°. The residue was treated with 5·75 g. of sodium, allowed to react overnight, 39 g. of ethyl iodide were added, and the mixture refluxed for 2 hours: this gave 35 g. of the crude ether, b. p. up to 150°. Repeated distillation over excess of sodium afforded 33 g. of pure ethyl *n*-hexyl ether, b. p. 142—143°/773 mm.

Diethyleneglycol diethyl ether (" *diethyl carbitol* "). The Carbon and Carbide Corporation product was first distilled from sodium, and the fraction, b. p. 185—187·5°/775 mm., collected. Redistillation from sodium gave the pure compound, b. p. 187—187·5°/775 mm.

Tetraethyleneglycol dimethyl ether (" *dimethoxy tetraglycol* "). The Carbon and Carbide Corporation product was treated with excess of sodium; when the vigorous reaction had subsided, the product was distilled and the fraction, b. p. 240—265°, collected. This was thrice distilled from sodium; there was considerable fuming at the end of the distillation, presumably owing to the vaporisation of the sodium. Finally, the alcohol-free product was distilled in the absence of sodium, and the liquid, b. p. 269—270°/767 mm., collected for the physical measurements.

Preparation of Phenyl Alkyl Ethers.—Anisole. 46·5 G. of pure phenol were added to a solution of 20 g. of A.R. sodium hydroxide contained in a 500-ml. three-necked flask equipped with a dropping-funnel, mechanical stirrer, and reflux condenser. The mixture was vigorously stirred; heat was evolved. 63 G. of methyl sulphate were slowly added during 1 hour, and the reaction mixture was refluxed, with stirring, for 14 hours. The cold mixture was diluted with water, and the anisole layer was separated and washed with water (addition of salt facilitated the complete removal of the water), twice with dilute sulphuric acid, and finally with water until the washings were neutral to litmus, and dried ($CaCl_2$). Distillation gave 42 g. of anisole, b. p. 150—153°. Upon redistillation, the anisole boiled constantly at 151°/736 mm. and a middle fraction was used for the physical measurements. This procedure is more convenient for the preparation of small quantities of anisole than that given in *Org. Synth.*, Coll. Vol. I, 1941, 58.

Phenetole. The procedure used was similar to that for phenyl *n*-propyl ether: the quantities employed were 11·5 g. of sodium in 250 ml. of absolute ethyl alcohol, 47 g. of A.R. phenol dissolved in 50 ml. of absolute ethyl alcohol, and 78 g. of colourless ethyl iodide. The yield of phenetole, b. p. 169°/766 mm., was 37 g.

Phenyl n-*propyl ether.* Into a 1-l. round-bottomed flask, fitted with a double-surface reflux condenser, were placed 11·5 g. of sodium and 250 ml. of absolute ethyl alcohol. When all the sodium had reacted, 47 g. of A.R. phenol dissolved in 50 ml. of absolute ethyl alcohol were added, followed by 107·5 g. of pure colourless *n*-propyl iodide. The mixture was refluxed for 4 hours, but no solid separated. Most of the alcohol was then distilled off on a water-bath: upon addition of excess of water to the distillate, 23 g. of the crude iodide were recovered. The residue in the flask was treated with water, and the upper layer was separated and washed successively with 10% sodium hydroxide solution (twice), water, dilute sulphuric acid (twice), and water (twice), and then dried ($MgSO_4$). Distillation gave 50 g. of phenyl *n*-propyl ether, b. p. 187°/751 mm.

Phenyl iso*propyl ether.* The quantities employed were 11·5 g. of sodium, 300 ml. of absolute ethyl alcohol, 47 g. of A.R. phenol, and 107·5 g. of pure *iso*propyl bromide: the mixture was refluxed for 5 hours. The yield of phenyl *iso*propyl ether, b. p. 174°/758 mm., was 27 g. About 6 g. of ether but no iodide were recovered from the alcohol distillate upon dilution with water.

Phenyl n-*butyl ether.* The quantities employed were 11·5 g. of sodium in 200 ml. of absolute ethyl alcohol, a solution of 47 g. of pure phenol in 50 ml. of absolute ethyl alcohol, and 133 g. of pure, colourless *n*-butyl iodide. The mixture was refluxed for 7 hours, and the alcohol distilled off until fuming commenced. Treatment of the residue with water, etc., gave 60 g. of phenyl *n*-butyl ether, b. p. 207·5°/755 mm.

Phenyl n-*amyl ether.* An excess of halide was not used in this preparation because the iodide and ether appear to form a mixture which passes over with the alcohol. The quantities employed were 11·5 g. of sodium in 250 ml. of absolute ethyl alcohol, a solution of 47 g. of A.R. phenol in 50 ml. of absolute alcohol, and 75·5 g. of *n*-amyl bromide. The mixture was refluxed for 8 hours and the excess of alcohol was distilled off from a water-bath. The residue was diluted with water, the crude phenyl *n*-amyl ether extracted with ether, washed with 10% sodium hydroxide solution, water, dilute sulphuric acid and water, dried ($MgSO_4$), and distilled: the yield of crude ether, b. p. 220—226° (mainly 225°), was 60 g. This was refluxed with 10 g. of sodium for 1 hour and considerable darkening occurred; the ether was distilled off and then fractionated from a little fresh sodium. The yield was 45 g.; b. p. 226·5°/751 mm. The large loss upon treatment with sodium is noteworthy; some reaction appears to take place. This was the only phenyl alkyl ether purified in this manner.

Phenyl n-*hexyl ether.* The quantities employed were 11·5 g. of sodium in 250 ml. of absolute alcohol, 47 g. of pure phenol in 50 ml. of absolute alcohol, and 82 g. of *n*-hexyl bromide. The mixture was refluxed for 6 hours and yielded, after working up as usual and two distillations, 60 g. of phenyl *n*-hexyl ether, b. p. 245·5°/761 mm.

Phenyl allyl ether. This was prepared by refluxing a mixture of 47 g. of A.R. phenol, 60·5 g. of allyl bromide (b. p. 70—71°/750 mm.), 70 g. of A.R. potassium carbonate, and 75 g. of A.R. acetone for 10 hours on a water-bath (compare Claisen, *Annalen*, 1918, **418**, 78), and pouring the product into excess of water. The upper layer was separated, dissolved in ether, washed twice with dilute sodium hydroxide solution and twice with water, and then dried ($MgSO_4$). After removal of the solvent, the liquid was distilled, and yielded 50 g. of crude phenyl allyl ether, b. p. 185—194° (largely 189—191°). Redistillation gave the pure ether, b. p. 190·5°/765 mm.

141. *Diethyl ether.* B. p. 34·0°/774 mm.; M 74·12; n_C 1·35079, n_D 1·35272, n_F 1·35701, $n_{G'}$ 1·35990; R_C 22·40, R_D 22·51, R_F 22·76, $R_{G'}$ 22·92; $Mn_D^{20°}$ 100·26. Densities determined: $d_{4°}^{20°}$ 0·7135, $d_{4°}^{23·6°}$ 0·7094. Apparatus *A*.

(These headings apply to corresponding columns in all the following tables.)

t.	*H.*	$d_{4°}^{t°}$.	γ.	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	γ.	*P.*
18·4°	12·88	0·7153	17·25	211·5	29·4°	12·35	0·7028	16·25	212·3
23·6	12·63	0·7094	16·78	212·0				Mean	211·9

142. *Di*-n-*propyl ether.* B. p. 90—90·5°/768 mm.; M 102·17; n_C 1·37862, n_D 1·38086, n_F 1·38553, $n_{G'}$ 1·38889; R_C 31·51, R_D 31·68, R_F 32·02, $R_{G'}$ 32·27; $Mn_D^{20°}$ 141·09. Densities determined: $d_{4°}^{20°}$ 0·7487, $d_{4°}^{40·5°}$ 0·7288, $d_{4°}^{61·1°}$ 0·7088. Apparatus *D*.

21·7°	11·02	0·7470	20·33	290·4	59·8°	9·32	0·7101	16·34	290·3
42·4	10·13	0·7262	18·17	290·5				Mean	290·4

143. *Diiso**propyl ether.* B. p. 68°/753 mm.; M 102·17; n_C 1·36637, n_D 1·36823, n_F 1·37262, $n_{G'}$ 1·37572; R_C 31·57, R_D 31·71, R_F 32·05, $R_{G'}$ 32·29; $Mn_D^{20°}$ 139·79. Densities determined: $d_{4°}^{20°}$ 0·7257, $d_{4°}^{40·7°}$ 0·7029, $d_{4°}^{68·1°}$ 0·6824. Apparatus *B*.

t.	*H.*	$d_4^{t°}$.	γ.	*P.*	*t.*	*N.*	$d_4^{t°}$.	γ.	*P.*
14·1°	10·71	0·7323	18·39	288·9	40·7°	9·51	0·7029	15·67	289·2
24·4	10·26	0·7208	17·34	289·3	56·7	8·68	0·6840	13·92	289·5
								Mean	289·2

144. *Di*-n-*butyl ether*. B. p. 141°/765 mm.; *M* 130·22; n_C 1·39685, n_D 1·39896, n_F 1·40387, $n_{G'}$ 1·40741; R_C 40·69, R_D 40·89, R_F 41·33, $R_{G'}$ 41·65; $Mn_D^{20°}$ 182·18. Densities determined: $d_4^{20°}$ 0·7704, $d_4^{40·8°}$ 0·7512, $d_4^{60·2°}$ 0·7342, $d_4^{85·7°}$ 0·7117. Apparatus *B*.

12·5°	12·82	0·7771	23·65	369·5	61·8°	10·85	0·7328	18·88	370·4
40·9	11·76	0·7511	20·97	370·9	85·7	9·98	0·7117	16·86	370·8
								Mean	370·4

145. *Di*-n-*amyl ether*. B. p. 184°/739 mm.; *M* 158·28; n_C 1·40983, n_D 1·41192, n_F 1·41703, $n_{G'}$ 1·42064; R_C 49·94, R_D 50·17, R_F 50·71, $R_{G'}$ 51·10; $Mn_D^{20°}$ 223·48. Densities determined: $d_4^{20°}$ 0·7849, $d_4^{40·6°}$ 0·7676, $d_4^{61·7°}$ 0·7506, $d_4^{86·4°}$ 0·7310. Apparatus *A*.

12·0°	17·26	0·7915	25·58	449·7	63·8°	14·74	0·7489	20·67	450·6
20·4	16·91	0·7846	24·84	450·7	87·5	13·66	0·7301	18·67	450·7
40·7	15·85	0·7675	22·78	450·4				Mean	450·4

146A. *Diisoamyl ether* (from Bisol fermentation *iso*amyl alcohol). B. p. 172°/762 mm.; *M* 158·28; n_C 1·40575, n_D 1·40785, n_F 1·41291, $n_{G'}$ 1·41656; R_C 50·05, R_D 50·28, R_F 50·82, $R_{G'}$ 51·22; $Mn_D^{20°}$ 222·84. Densities determined: $d_4^{20°}$ 0·7765, $d_4^{61·2°}$ 0·7433, $d_4^{86·5°}$ 0·7221, $d_4^{121·8°}$ 0·6941. Apparatus *A*.

15·1°	16·05	0·7805	23·46	446·3	87·3°	12·71	0·7215	17·23	446·7
24·4	15·66	0·7729	22·66	446·8	119·5	11·20	0·6960	14·60	444·5
61·0	13·95	0·7435	19·42	446·9				Mean	446·2

146B. *Diisoamyl ether* (from Sharples synthetic *iso*amyl alcohol). B. p. 171°/758 mm.; *M* 158·28; n_C 1·40642, n_D 1·40850, n_F 1·41355, $n_{G'}$ 1·41716; R_C 50·04, R_D 50·27, R_F 50·82, $R_{G'}$ 51·21; $Mn_D^{20°}$ 222·94. Densities determined: $d_4^{20°}$ 0·7777, $d_4^{41·8°}$ 0·7605, $d_4^{63·3°}$ 0·7438, $d_4^{87·6°}$ 0·7237. Apparatus *A*.

21·7°	15·72	0·7763	22·85	445·8	60·3°	13·86	0·7462	19·37	445·0
28·0	15·45	0·7713	22·31	446·0	86·2	12·70	0·7243	17·22	445·2
40·1	14·95	0·7619	21·33	446·4				Mean	445·7

147. *Di*-n-*hexyl ether*. B. p. 223°/763 mm.; *M* 186·33; n_C 1·41829, n_D 1·42041, n_F 1·42560, $n_{G'}$ 1·42943; R_C 59·22, R_D 59·48, R_F 60·12, $R_{G'}$ 60·59; $Mn_D^{20°}$ 264·66. Densities determined: $d_4^{20°}$ 0·7934, $d_4^{40·2°}$ 0·7782, $d_4^{61·6°}$ 0·7628, $d_4^{86·9°}$ 0·7435. Apparatus *A*.

21·4°	17·26	0·7924	25·61	529·0	62·3	15·59	0·7623	22·25	530·9
25·3	17·19	0·7894	25·41	529·9	86·0	14·41	0·7442	20·08	530·0
41·7	16·39	0·7771	23·85	529·9				Mean	529·9

148. *Di*-n-*heptyl ether*. B. p. 258·5°/769; *M* 214·38; n_C 1·42531, n_D 1·42747, n_F 1·43281, $n_{G'}$ 1·43669; R_C 68·50, R_D 68·81, R_F 69·55, $R_{G'}$ 70·09; $Mn_D^{20°}$ 306·03. Densities determined: $d_4^{20°}$ 0·8008, $d_4^{40·6°}$ 0·7869, $d_4^{60·7°}$ 0·7728, $d_4^{86·9°}$ 0·7537. Apparatus *D*.

16·2°	13·79	0·8034	27·36	610·3	43·4°	12·91	0·7850	25·03	610·7
19·2	13·65	0·8014	27·02	609·9	62·1	12·26	0·7718	23·37	610·7
29·9	13·33	0·7940	26·14	610·5	86·0	11·49	0·7531	21·37	612·1
								Mean	610·7

149. *Di*-n-*octyl ether*. B. p. 288°/778 mm.; *M* 242·43; n_C 1·43049, n_D 1·43269, n_F 1·43803, $n_{G'}$ 1·44199; R_C 77·75, R_D 78·10, R_F 78·93, $R_{G'}$ 79·56; $Mn_D^{20°}$ 347·34. Densities determined: $d_4^{20°}$ 0·8063, $d_4^{41·5°}$ 0·7920, $d_4^{62·3°}$ 0·7781, $d_4^{86·6°}$ 0·7612. Apparatus *A*.

25·4°	18·13	0·8027	27·25	690·0	61·4°	16·63	0·7787	24·25	691·7
41·3	17·50	0·7922	26·02	691·2	85·6	15·63	0·7617	22·29	691·6
								Mean	691·1

150. *Methyl* n-*butyl ether*. B. p. 70·5°/766 mm.; *M* 88·15; n_C 1·37179, n_D 1·37364, n_F 1·37819, $n_{G'}$ 1·38138; R_C 26·90, R_D 27·02, R_F 27·32, $R_{G'}$ 27·52; $Mn_D^{20°}$ 121·08. Densities determined: $d_4^{20°}$ 0·7443, $d_4^{41·4°}$ 0·7237. Apparatus *A*.

17·0°	14·52	0·7472	20·32	250·7	26·5°	14·12	0·7381	19·52	251·3
18·3	14·46	0·7459	20·20	250·7	40·9	13·12	0·7242	17·79	250·4
								Mean	250·8

151. *Ethyl* n-*butyl ether*. B. p. 91·5°/757 mm.; *M* 102·17; n_C 1·37983, n_D 1·38175, n_F 1·38645, $n_{G'}$ 1·38965; R_C 31·58, R_D 31·73, R_F 32·08, $R_{G'}$ 32·31; $Mn_D^{20°}$ 141·18. Densities determined: $d_4^{20°}$ 0·7490, $d_4^{40·9°}$ 0·7298, $d_4^{58·0°}$ 0·7132. Apparatus *A*.

16·0°	14·93	0·7527	21·04	290·7	42·3°	13·42	0·7285	18·31	290·4
18·3	14·85	0·7506	20·87	290·9	59·3	12·40	0·7120	16·53	289·8
								Mean	290·5

152. *Methyl* n-*amyl ether.* B. p. 99°/763 mm.; M 102·17; n_C 1·38534, n_D 1·38729, n_F 1·39213, $n_{G'}$ 1·39543; R_C 31·50, R_D 31·65, R_F 31·99, $R_{G'}$ 32·24; $Mn_D^{20°}$ 141·74. Densities determined: $d_{4°}^{20°}$ 0·7606, $d_{4°}^{41·4°}$ 0·7406, $d_{4°}^{60·1°}$ 0·7229. Apparatus *D*.

t.	*H.*	$d_{4°}^{t°}$	*γ.*	*P.*	*t.*	*H.*	$d_{4°}^{t°}$	*γ.*	*P.*
18·0°	11·74	0·7625	22·11	290·5	42·0°	10·74	0·7400	19·63	290·8
24·0	11·50	0·7568	21·49	290·7	60·1	9·93	0·7229	17·73	290·4
								Mean	290·6

153. *Ethyl* n-*amyl ether.* B. p. 117·5—118·5°/768 mm.; M 116·20; n_C 1·39071, n_D 1·39270, n_F 1·39753, $n_{G'}$ 1·40097; R_C 36·20, R_D 36·36, R_F 36·75, $R_{G'}$ 37·04; $Mn_D^{20°}$ 161·83. Densities determined: $d_{4°}^{20°}$ 0·7622, $d_{4°}^{41·4°}$ 0·7428, $d_{4°}^{60·5°}$ 0·7260, $d_{4°}^{85·5°}$ 0·7019. Apparatus *A*.

16·5°	15·72	0·7654	22·53	330·8	41·7°	14·38	0·7425	20·45	330·9
19·1	15·48	0·7630	22·12	330·3	61·9	13·26	0·7247	17·99	330·6
26·5	15·18	0·7563	21·50	330·8	86·8	11·81	0·7007	15·50	329·7
								Mean	330·5

154. *Methyl* n-*hexyl ether.* B. p. 126°/770 mm.; M 116·20; n_C 1·39520, n_D 1·39719, n_F 1·40207, $n_{G'}$ 1·40551; R_C 36·10, R_D 36·26, R_F 36·65, $R_{G'}$ 36·93; $Mn_D^{20°}$ 162·35. Densities determined: $d_{4°}^{20°}$ 0·7721, $d_{4°}^{41·6°}$ 0·7532, $d_{4°}^{61·7°}$ 0·7356, $d_{4°}^{86·7°}$ 0·7129. Apparatus *A*.

14·3°	16·34	0·7771	23·78	330·2	41·5°	14·89	0·7533	21·00	330·2
17·0	16·17	0·7747	32·46	330·1	61·6	13·82	0·7357	19·04	330·0
24·3	15·91	0·7683	22·89	330·8	85·9	12·51	0·7136	16·72	329·7
26·5	15·77	0·7664	22·63	330·7				Mean	330·2

155. *Ethyl* n-*hexyl ether.* B. p. 142—143°/773 mm.; M 130·22; n_C 1·39881, n_D 1·40082, n_F 1·40576, $n_{G'}$ 1·40936; R_C 40·77, R_D 40·95, R_F 41·41, $R_{G'}$ 41·73; $Mn_D^{20°}$ 182·41. Densities determined: $d_{4°}^{20°}$ 0·7722, $d_{4°}^{41·2°}$ 0·7541, $d_{4°}^{61·1°}$ 0·7373, $d_{4°}^{87·0°}$ 0·7138. Apparatus *D*.

14·5°	12·39	0·7770	22·08	370·1	61·4°	10·50	0·7370	19·11	369·4
42·1	11·29	0·7533	21·00	370·6	87·7	9·46	0·7132	16·66	369·0
								Mean	369·8

156. 2 : 2′-*Dichlorodiethyl ether.* B. p. 178°/744 mm.; M 143·02; n_C 1·45475, n_D 1·45717, n_F 1·46305, $n_{G'}$ 1·46744; R_C 31·80, R_D 31·94, R_F 32·30, $R_{G'}$ 32·55; $Mn_D^{20°}$ 207·45. Densities determined: $d_{4°}^{20°}$ 1·2199, $d_{4°}^{41·6°}$ 1·1953, $d_{4°}^{61·0°}$ 1·1731, $d_{4°}^{86·7°}$ 1·1436. Apparatus *D*.

14·9°	12·75	1·2257	38·59	290·8	42·3°	11·87	1·1947	35·02	291·2
19·3	12·57	1·2207	37·89	290·7	61·9	11·26	1·1721	32·59	291·6
26·1	12·43	1·2127	37·23	291·3	86·6	10·46	1·1437	29·54	291·6
								Mean	291·2

157. *Diethyleneglycol diethyl ether* ("*diethyl carbitol*"). B. p. 187—187·5°/775 mm.; M 162·22; n_C 1·40940, n_D 1·41147, n_F 1·41648, $n_{G'}$ 1·42007; R_C 44·29, R_D 44·49, R_F 44·97, $R_{G'}$ 45·31; $Mn_D^{20°}$ 228·97. Densities determined: $d_{4°}^{20°}$ 0·9063, $d_{4°}^{42·0°}$ 0·8863, $d_{4°}^{60·1°}$ 0·8690, $d_{4°}^{87·1°}$ 0·8435. Apparatus *A*.

15·9°	16·21	0·9101	27·62	408·6	42·1°	15·09	0·8862	25·10	409·5
22·1	15·94	0·9043	26·99	408·9	63·2	14·10	0·8661	22·87	409·6
26·1	15·82	0·9006	26·68	409·1	87·9	11·99	0·8427	18·92	410·8
								Mean	409·4

158. *Tetraethyleneglycol dimethyl ether* ("*dimethoxy tetraglycol*"). B. p. 266—267°/767 mm. (uncorr.); M 222·28; n_C 1·43032, n_D 1·43249, n_F 1·43782, $n_{G'}$ 1·44171; R_C 56·96, R_D 57·21, R_F 57·82, $R_{G'}$ 58·27; $Mn_D^{20°}$ 318·42. Densities determined: $d_{4°}^{20°}$ 1·0087, $d_{4°}^{41·4°}$ 0·9912, $d_{4°}^{60·2°}$ 0·9749, $d_{4°}^{85·7°}$ 0·9514. Apparatus *D*.

20·5°	13·58	1·0083	33·84	531·6	60·7°	12·38	0·9745	29·79	532·9
41·9	12·96	0·9908	31·71	532·4	86·3	11·56	0·9509	27·15	533·6
								Mean	532·6

159. *Anisole.* B. p. 151°/736 mm.; M 108·13; n_C 1·51298, n_D 1·51779, n_F 1·53043, $n_{G'}$ 1·54061; R_C 32·63, R_D 32·88, R_F 33·55, $R_{G'}$ 34·09; $Mn_D^{20°}$ 164·12. Densities determined: $d_{4°}^{20°}$ 0·9961, $d_{4°}^{60·4°}$ 0·9585 $d_{4°}^{86·7°}$ 0·9339, $d_{4°}^{120·9°}$ 0·9010. Apparatus *A*.

13·4°	19·46	1·0022	36·52	265·2	87·1°	15·71	0·9335	27·46	265·2
23·7	19·03	0·9927	35·37	265·6	120·3	14·09	0·9016	23·79	265·3
61·5	17·08	0·9575	30·57	265·5				Mean	265·4

160. *Phenetole.* B. p. 169°/766 mm.; M 122·16; n_C 1·50283, n_D 1·50736, n_F 1·51905, $n_{G'}$ 1·52877; R_C 37·42, R_D 37·70, R_F 38·44, $R_{G'}$ 39·04; $Mn_D^{20°}$ 184·14. Densities determined: $d_{4°}^{20°}$ 0·9648, $d_{4°}^{4·00°}$ 0·9472, $d_{4°}^{59·6°}$ 0·9295, $d_{4°}^{86·9°}$ 0·9040. Apparatus *C*.

18·9°	14·49	0·9658	33·15	304·1	61·2°	12·83	0·9290	28·30	303·3
22·0	14·37	0·9630	32·85	303·7	86·8	11·98	0·9041	25·71	304·3
40·2	13·59	0·9470	30·55	303·3				Mean	303·7

161. *Phenyl* n-*propyl ether.* B. p. 187°/751 mm.; *M* 136·19; n_C 1·49705, n_D 1·51034, n_F 1·51228, $n_{G'}$ 1·52127; R_C 41·98, R_D 42·28, R_F 43·07, $R_{G'}$ 43·70; $Mn_D^{20°}$ 204·26. Densities determined: $d_{4°}^{20°}$ 0·9494, $d_{4°}^{41·2°}$ 0·9312, $d_{4°}^{60·6°}$ 0·9141, $d_{4°}^{86·2°}$ 0·8914. Apparatus *A*.

t.	*H.*	$d_{4°}^{t°}$.	*γ.*	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	*γ.*	*P.*
19·5°	18·11	0·9498	32·21	341·6	61·5°	16·23	0·9133	27·76	342·3
25·8	17·85	0·9453	31·60	341·6	86·7	15·06	0·8910	25·13	342·2
41·5	17·13	0·9309	29·86	342·0				Mean	341·9

162. *Phenyl* iso*propyl ether.* B. p. 174°/758 mm.; *M* 136·19; n_C 1·49328, n_D 1·49753, n_F 1·50837, $n_{G'}$ 1·51732; R_C 42·09, R_D 42·39, R_F 43·18, $R_{G'}$ 43·81; $Mn_D^{20°}$ 203·95. Densities determined: $d_{4°}^{20°}$ 0·9408, $d_{4°}^{41·0°}$ 0·9221, $d_{4°}^{60·1°}$ 0·9037, $d_{4°}^{85·2°}$ 0·8805. Apparatus *A*.

18·9°	17·53	0·9418	30·91	341·0	61·0°	15·62	0·9029	26·41	341·9
25·2	17·33	0·9360	30·37	341·6	86·0	14·52	0·8798	23·92	342·3
40·7	16·55	0·9224	28·58	341·4				Mean	341·6

163. *Phenyl* n-*butyl ether.* B. p. 207·5°/755 mm.; *M* 150·21; n_C 1·49297, n_D 1·49708, n_F 1·50747, $n_{G'}$ 1·51603; R_C 46·73, R_D 47·06, R_F 47·90, $R_{G'}$ 48·57; $Mn_D^{20°}$ 224·88. Densities determined: $d_{4°}^{20°}$ 0·9341, $d_{4°}^{41·8°}$ 0·9169, $d_{4°}^{61·5°}$ 0·9002, $d_{4°}^{85·8°}$ 0·8793. Apparatus *A*.

18·7°	18·09	0·9352	31·68	381·1	60·9°	16·28	0·9007	27·46	381·7
25·4	17·72	0·9297	30·85	380·8	86·4	15·24	0·8788	25·08	382·5
40·4	17·13	0·9179	29·44	381·2				Mean	381·7

164. *Phenyl* n-*amyl ether.* B. p. 226·5°/751 mm.; *M* 164·24; n_C 1·49074, n_D 1·49469, n_F 1·50466, $n_{G'}$ 1·51239; R_C 51·28, R_D 51·64, R_F 52·52, $R_{G'}$ 53·20; $Mn_D^{20°}$ 245·49. Densities determined: $d_{4°}^{20°}$ 0·9270, $d_{4°}^{39·9°}$ 0·9111, $d_{4°}^{60·0°}$ 0·8948, $d_{4°}^{84·3°}$ 0·8756. Apparatus *E*.

14·7°	14·58	0·9312	32·23	420·2	60·3°	13·15	0·8946	27·93	422·0
41·3	13·77	0·9100	29·75	421·5	87·7	12·25	0·8729	25·39	422·3
								Mean	421·5

165. *Phenyl* n-*hexyl ether.* B. p. 244·5°/761 mm.; *M* 178·26; n_C 1·48825, n_D 1·49203, n_F 1·50166, $n_{G'}$ 1·50938; R_C 56·00, R_D 56·38, R_F 57·32, $R_{G'}$ 58·06; $Mn_D^{20°}$ 265·99. Densities determined: $d_{4°}^{20°}$ 0·9174, $d_{4°}^{40·5°}$ 0·9024, $d_{4°}^{60·9°}$ 0·8872, $d_{4°}^{86·7°}$ 0·8670. Apparatus *D*.

17·3°	13·82	0·9193	31·38	459·0	61·5°	12·60	0·8868	27·59	460·8
24·5	13·68	0·9141	30·88	459·8	86·9	11·85	0·8669	25·37	461·5
41·3	13·22	0·9018	29·44	460·5				Mean	460·3

166. *Phenyl allyl ether.* B. p. 190·5°/765 mm.; *M* 134·17; n_C 151746, n_D 1·52232, n_F 1·53480, $n_{G'}$ 1·54475; R_C 41·41, R_D 41·73, R_F 42·68, $R_{G'}$ 43·23; $Mn_D^{20°}$ 204·25. Densities determined: $d_{4°}^{20°}$ 0·9811, $d_{4°}^{42·4°}$ 0·9609, $d_{4°}^{62·0°}$ 0·9439, $d_{4°}^{86·5°}$ 0·9212. Apparatus *D*.

18·0°	14·00	0·9829	33·98	329·6	41·5°	13·28	0·9617	31·54	330·6
25·4	13·87	0·9762	33·44	330·5	86·9	11·69	0·9208	26·58	330·9
								Mean	330·4

Ethers derived from Formaldehyde and Acetaldehyde.—Methylal. The commercial product was repeatedly refluxed and distilled from sodium until the latter was unaffected; b. p. 41·5°/754 mm.

Ethylal. The commercial product was shaken with a mixture of " 20-volume " hydrogen peroxide and 2% sodium carbonate solution at 40—45° (compare Adams, *J. Amer. Chem. Soc.*, 1925, **47**, 1366), then twice with water, dried (K_2CO_3), and refluxed with and finally distilled from sodium; b. p. 86·5—87°/749 mm.

n-*Propylal.* The commercial product was purified as under ethylal; b. p. 136·5°/751 mm.

n-*Butylal.* The following modification of Trillatt and Cambier's method (*Bull. Soc. chim.*, 1894, **11**, 754) was employed. A mixture of 15 g. of pure paraformaldehyde, 74 g. of pure *n*-butyl alcohol, and 2 g. of A.R. anhydrous ferric chloride was refluxed for 10 hours. The lower layer (3—4 ml.) was discarded and the iron in solution in the residue was removed as ferric hydroxide by shaking with 50 ml. of 10% sodium carbonate solution; the product was shaken with a mixture of 40 ml. of " 20-volume " hydrogen peroxide and 5 ml. of 10% sodium carbonate solution at 45° (to remove any residual aldehyde), washed with water, and dried (K_2CO_3). Distillation from excess of sodium yielded 62 g. of crude *n*-butylal, b. p. 170—185°. Repeated refluxing with and distillation from sodium gave the pure ether of b. p. 180·5°/760 mm.

iso*Butylal.* A mixture of 15 g. of paraformaldehyde, 74 g. of pure *iso*butyl alcohol, and 2 g. of anhydrous ferric chloride yielded, as for *n*-butylal, 57 g. of crude *iso*butylal, b. p. 155—170°. Repeated distillation over sodium gave the pure compound, b. p. 163·5—164°/766 mm.

n-*Amylal.* A mixture of 15 g. of paraformaldehyde, 88 g. of *n*-amyl alcohol (b. p. 137°/733 mm.), and 2 g. of A.R. anhydrous ferric chloride gave, as before, 55 g. of crude *n*-amylal, b. p. 210—220°. Repeated distillation from sodium afforded the pure compound, b. p. 218·5—219°/761 mm.

n-*Hexylal.* A mixture of 15 g. of paraformaldehyde, 102 g. of *n*-hexyl alcohol (b. p. 156—157°/752 mm.), and 2 g. of anhydrous ferric chloride gave 75 g. of crude *n*-hexylal, b. p. 253—260°. Two distillations from sodium yielded the pure compound, b. p. 255—255·5°/770 mm.

iso*Propylal.* A mixture of 15 g. of paraformaldehyde, 60 g. of pure *iso*propyl alcohol and 2 g. of A.R. anhydrous ferric chloride furnished 28 g. of crude *iso*propylal, b. p. 119—123°. The pure compound, b. p. 120·5—121°/765 mm., was obtained after two distillations from sodium.

Dimethyl acetal, $CH_3{\cdot}CH(OCH_3)_2$. The pure commercial product was treated with alkaline hydrogen peroxide solution at 40—45° (owing to the solubility of the compound in water, it was necessary to saturate the solution with salt), dried (K_2CO_3), and distilled from sodium; b. p. 64°/762 mm.

Diethyl acetal. The commercial product was purified as for dimethyl acetal; b. p. 102·5°/755 mm.

Di-n-propyl acetal. A mixture of 44 g. of paraldehyde, 150 g. of pure *n*-propyl alcohol, and 4 g. of *p*-toluenesulphonic acid was refluxed for 8 hours. The excess of acid was removed by washing with a solution containing 2·5 g. of anhydrous sodium carbonate; shaking with a mixture of 50 ml. of " 20-volume " hydrogen peroxide and 10 ml. of 10% sodium carbonate solution at 40—45° removed any residual aldehyde. The product was dried (K_2CO_3) and fractionally distilled: 89 g. of unchanged alcohol were recovered at 88—101° and the yield of crude acetal, b. p. 142—148°, was 52 g. Two distillations from sodium gave the pure compound, b. p. 147—147·5°/760 mm.

Di-n-butyl acetal. A mixture of 44 g. of paraldehyde, 187·5 g. of pure *n*-butyl alcohol, and 5 g. of *p*-toluenesulphonic acid yielded, as detailed for di-*n*-propyl acetal, 67 g. of unreacted, but impure, *n*-butyl alcohol, b. p. 110—120°, and 115 g. of crude di-*n*-butyl acetal, b. p. 181—188°. Two distillations from sodium afforded the pure acetal, b. p. 187·5°/774 mm.

Diisobutyl acetal. The reaction between 33 g. of paraldehyde, 127 g. of pure *iso*butyl alcohol, and 3 g. of *p*-toluenesulphonic acid yielded, as detailed for di-*n*-propyl acetal, 41 g. of impure unreacted *iso*butyl alcohol, b. p. 105—115°, and 70 g. of crude di*iso*butyl acetal, b. p. 167—170°. The pure acetal, b. p. 169·5—170°/757 mm., was obtained after one distillation from sodium.

167. *Methylal.* B. p. 41·5°/754 mm.; M 60·09; n_C 1·35134, n_D 1·35298, n_F 1·35704, $n_{G'}$ 1·35986; R_C 19·12, R_D 19·20, R_F 19·40, $R_{G'}$ 19·54; $Mn_D^{20°}$ 102·95. Densities determined: $d_{4°}^{20·6°}$ 0·8593, $d_{4°}^{14·0°}$ 0·8669. Apparatus *A*.

t.	*H.*	$d_{4°}^{t°}$.	γ.	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	γ.	*P.*
14·5°	13·52	0·8661	21·93	190·4	24·2°	12·91	0·8541	20·65	190·3
18·5	13·23	0·8612	21·33	190·3				Mean	190·3

168. *Ethylal.* B. p. 86·5—87°/749 mm.; M 104·15; n_C 1·37072, n_D 1·37262, n_F 1·37691, $n_{G'}$ 1·37996; R_C 28·40, R_D 28·53, R_F 28·83, $R_{G'}$ 29·04; $Mn_D^{20°}$ 142·96. Densities determined: $d_{4°}^{20°}$ 0·8308, $d_{4°}^{40·2°}$ 0·8094, $d_{4°}^{59·8°}$ 0·7893. Apparatus *A*.

18·5°	13·74	0·8323	21·41	269·2	40·7°	12·53	0·8089	18·98	269·0
21·1	13·55	0·8297	21·05	268·9	59·7	11·49	0·7889	15·97	268·5
								Mean	268·9

169. n-*Propylal.* B. p. 136·5°/751 mm.; M 132·20, n_C 1·39068, n_D 1·39261, n_F 1·39728, $n_{G'}$ 1·40056; R_C 37·64, R_D 37·80, R_F 38·20, $R_{G'}$ 38·48; $Mn_D^{20°}$ 184·07. Densities determined: $d_{4°}^{20°}$ 0·8338, $d_{4°}^{40·9°}$ 0·8139, $d_{4°}^{59·8°}$ 0·7974, $d_{4°}^{85·1°}$ 0·7716. Apparatus *D*.

16·6°	11·44	0·8360	23·62	348·6	60·0°	9·88	0·7963	19·43	348·5
21·3	11·27	0·8326	23·17	348·3	85·1	8·94	0·7716	17·11	348·0
40·7	10·55	0·8141	21·21	348·4				Mean	348·4

170. n-*Butylal.* B. p. 180·5°/760 mm.; M 160·25; n_C 1·40374, n_D 1·40573, n_F 1·41062, $n_{G'}$ 1·41410; R_C 46·89, R_D 47·09, R_F 47·59, $R_{G'}$ 47·95; $Mn_D^{20°}$ 225·27. Densities determined: $d_{4°}^{20°}$ 0·8354, $d_{4°}^{40·8°}$ 0·8191, $d_{4°}^{60·9°}$ 0·8023, $d_{4°}^{85·9°}$ 0·7813. Apparatus *A*.

17·4°	15·77	0·8375	24·74	426·7	40·7	14·82	0·8187	22·72	427·3
22·7	15·62	0·8332	24·37	427·3	61·5	13·93	0·8018	20·87	427·4
25·5	15·54	0·8309	24·18	427·7	86·4	12·83	0·7809	18·76	427·1
								Mean	427·3

171. iso*Butylal.* B. p. 163·5—164°/766 mm.; M 160·25; n_C 1·39833, n_D 1·40029, n_F 1·40515, $n_{G'}$ 1·40868; R_C 46·95, R_D 47·15, R_F 47·66, $R_{G'}$ 48·02; $Mn_D^{20°}$ 224·40. Densities determined: $d_{4°}^{20°}$ 0·8244, $d_{4°}^{41·1°}$ 0·8063, $d_{4°}^{61·5°}$ 0·7886, $d_{4°}^{87·0°}$ 0·7654. Apparatus *A*.

21·0°	14·64	0·8235	22·57	424·2	61·3°	12·85	0·7888	18·98	424·0
40·9	13·77	0·8065	20·80	424·3	87·0	11·74	0·7654	16·83	424·0
								Mean	424·1

172. n-*Amylal.* B. p. 218·5—219°/761 mm.; M 188·30; n_C 1·41419, n_D 1·41626, n_F 1·42127, $n_{G'}$ 1·42489; R_C 56·13, R_D 56·38, R_F 56·97, $R_{G'}$ 57·40; $Mn_D^{20°}$ 266·69. Densities determined: $d_{4°}^{20°}$ 0·8387, $d_{4°}^{41·0°}$ 0·8221, $d_{4°}^{60·9°}$ 0·8066, $d_{4°}^{85·9°}$ 0·7868. Apparatus *D*.

16·3°	12·68	0·8416	26·35	506·9	41·4°	11·85	0·8219	24·00	507·1
19·8	12·51	0·8389	25·92	506·5	60·8	11·14	0·8067	22·19	506·6
23·3	12·41	0·8361	25·62	506·6	87·2	10·38	0·7858	19·68	504·8
								Mean	506·4

173. n-*Hexylal.* B. p. 255—255·5°/770 mm.; M 216·35; n_C 1·42130, n_D 1·42341, n_F 1·42856, $n_{G'}$ 1·43216; R_C 65·26, R_D 65·55, R_F 66·25, $R_{G'}$ 66·74; $Mn_D^{20°}$ 307·95. Densities determined: $d_{4°}^{20°}$ 0·8412, $d_{4°}^{40·7°}$ 0·8255, $d_{4°}^{62·0°}$ 0·8098, $d_{4°}^{86·1°}$ 0·7912. Apparatus *D*.

17·4°	13·11	0·8432	27·30	586·5	61·9°	11·72	0·8099	23·44	587·8
21·0	12·98	0·8404	26·90	586·5	87·0	10·95	0·7905	21·38	588·5
41·3	12·37	0·8250	25·20	587·6				Mean	587·4

174. iso*Propylal.* B. p. 120·5—121°/765 mm.; *M* 132·20; n_C 1·38227, n_D 1·38413, n_F 1·38870, $n_{G'}$ 1·39194; R_C 37·64, R_D 37·79, R_F 38·19, $R_{G'}$ 38·47; $Mn_D^{20°}$ 182·98. Densities determined: $d_{4°}^{20°}$ 0·8181, $d_4^{43·2}$ 0·7965, $d_{4°}^{81·7°}$ 0·7786, $d_{4°}^{86·6°}$ 0·7536. Apparatus *D*.

t.	*H.*	$d_{4°}^{t°}$.	*γ.*	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	*γ.*	*P.*
20·3°	10·39	0·8178	20·98	346·0	59·9°	9·07	0·7794	17·46	346·7
22·1	10·32	0·8160	20·80	346·0	86·3	8·13	0·7539	15·14	346·5
41·4	9·64	0·7982	19·00	345·8				Mean	346·2

175. *Dimethyl acetal,* $CH_3{\cdot}CH(OCH_3)_2$. B. p. 64°/762 mm.; *M* 90·12; n_C 1·36472, n_D 1·36646, n_F 1·37066, $n_{G'}$ 1·37359; R_C 23·63, R_D 23·73, R_F 23·98, $R_{G'}$ 24·14; $Mn_D^{20°}$ 123·15. Densities determined: $d_{4°}^{20°}$ 0·8516, $d_{4°}^{41·0°}$ 0·8279, $d_{4°}^{60·4°}$ 0·8063. Apparatus *D*.

15·3°	10·45	0·8569	22·11	228·1	41·3°	9·33	0·8276	19·07	228·0
20·0	10·27	0·8516	21·60	228·1	60·1	8·51	0·8066	16·95	227·5
26·1	10·02	0·8447	20·90	228·1				Mean	228·0

176. *Diethyl acetal.* B. p. 102·5°/755 mm.; *M* 118·17; n_C 1·37871, n_D 1·38054, n_F 1·38502, $n_{G'}$ 1·38821; R_C 33·02, R_D 33·16, R_F 33·51, $R_{G'}$ 33·76; $Mn_D^{20°}$ 163·13. Densities determined: $d_{4°}^{20°}$ 0·8264, $d_{4°}^{41·6°}$ 0·8042, $d_{4°}^{60·5°}$ 0·7843, $d_{4°}^{86·3°}$ 0·7566. Apparatus *D*.

15·0°	10·72	0·8316	22·02	307·8	41·5°	9·59	0·8043	19·05	306·9
18·0	10·55	0·8285	21·59	307·5	60·9	8·82	0·7839	17·07	306·9
21·8	10·44	0·8245	21·26	307·7	86·3	7·86	0·7566	14·69	306·7
								Mean	307·3

177. *Di-*n*-propyl acetal.* B. p. 147—147·5°/760 mm.; *M* 146·22; n_C 1·39476, n_D 1·39670, n_F 1·40142, $n_{G'}$ 1·40470; R_C 42·19, R_D 42·37, R_F 42·81, $R_{G'}$ 43·13; $Mn_D^{20°}$ 204·23. Densities determined: $d_{4°}^{20°}$ 0·8304, $d_{4°}^{41·3°}$ 0·8096, $d_{4°}^{60·6°}$ 0·7914, $d_{4°}^{86·3°}$ 0·7665. Apparatus *A*.

12·4°	15·22	0·8378	23·88	385·8	41·5°	13·78	0·8094	20·88	386·2
17·3	15·00	0·8330	23·40	386·1	60·3	12·85	0·7919	19·05	385·8
20·2	14·85	0·8302	23·09	386·1	88·3	11·57	0·7646	16·56	385·8
								Mean	386·0

178. *Di-*n*-butyl acetal.* B. p. 187·5°/774 mm.; *M* 174·28; n_C 1·40650, n_D 1·40850, n_F 1·41333, $n_{G'}$ 1·41698; R_C 51·45, R_D 51·68, R_F 52·21, $R_{G'}$ 52·62; $Mn_D^{20°}$ 245·47. Densities determined: $d_{4°}^{20°}$ 0·8329, $d_4^{41·8°}$ 0·8147, $d_{4°}^{61·1°}$ 0·7989, $d_{4°}^{85·4°}$ 0·7779. Apparatus *A*.

15·2°	15·81	0·8372	24·78	464·5	41·3°	14·72	0·8151	22·47	465·4
91·3	15·67	0·8338	24·47	464·9	62·1	13·69	0·7981	20·46	464·4
22·0	15·58	0·8315	24·26	465·2	86·1	12·63	0·7773	18·38	464·3
								Mean	464·8

179. *Diiso*butyl *acetal.* B. p. 169·5—170°/757 mm.; *M* 174·28; n_C 1·40060, n_D 1·40258, n_F 1·40745, $n_{G'}$ 1·41085; R_C 51·52, R_D 51·75, R_F 52·31, $R_{G'}$ 52·69; $Mn_D^{20°}$ 244·45. Densities determined: $d_{4°}^{20°}$ 0·8211, $d_{4°}^{44·4°}$ 0·7997, $d_{4°}^{61·6°}$ 0·7847, $d_{4°}^{85·9°}$ 0·7626. Apparatus *A*.

16·3°	14·74	0·8244	22·75	461·7	61·0°	12·77	0·7852	18·78	462·0
22·3	14·48	0·8191	22·21	461·9	85·8	11·60	0·7627	16·57	461·0
41·3	13·62	0·8024	20·46	462·0				Mean	461·7

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130. *Physical Properties and Chemical Constitution. Part XIII. Aliphatic Carboxylic Esters.*

By ARTHUR I. VOGEL.

New measurements have been made of the parachors and refractivities of alkyl esters of formic, acetic, propionic, *n*-butyric, *iso*butyric, *n*-valeric, *iso*valeric, *n*-hexoic, *n*-heptoic, *n*-octoic, and *n*-dodecoic acids and the dialkyl esters of oxalic, succinic, adipic, suberic, and sebacic acids. The experimental data have been employed to compute, with the aid of the experimental figures for the aliphatic hydrocarbons (Part IX, *J.*, 1946, 133) and the values for alkyl groups deduced from them (Part XI, this vol., p. 610), the contributions of the CO·O group. The mean values for this, excluding the formates, oxalates, and malonates, are:

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
CO·O	63·4	6·173	6·200	6·261	6·315	64·14
O_2 (in esters)	54·8	3·601	3·609	3·660	3·660	38·43

If the values for C (Part IX, *loc. cit.*) are subtracted, the figures for O_2 (in carboxylic esters) are obtained. The value for O_2 of the parachor differs from that of Sugden (60·0) and the refractivities differ from the figures deduced by Eisenlohr (*Z. physikal. Chem.*, 1910, **75**, 585). Furthermore, if one combines the figures for the carbonyl group (Part XI) and for O in ethers (*not* acetals) (Part XII, preceding paper), the following results are obtained :

	P.	R_C.	R_D.	R_F.	R_G.	$Mn_D^{20°}$.
CO	45·9	4·684	4·713	4·768	4·830	42·38
O (in ethers)	19·8	1·753	1·764	1·786	1·805	22·74
CO + O (in ethers) -	65·7	6·437	6·477	6·554	6·635	65·12

The values for CO + O (ethers) are not identical with those deduced for CO·O from esters; Eisenlohr's assumption that

$$O_2 \text{ (esters)} = O'' \text{ (ketones)} + O< \text{ (ethers)}$$

therefore has no experimental foundation.

New experimental data are also provided for the parachors and refractivities of the dialkyl esters of methyl-, ethyl-, *n*-propyl-, and *n*-amyl-malonic acids. These figures differ (in most cases by quantities in excess of the experimental error) from those of the isomeric esters of the polymethylene carboxylic acids.

THE main objects of this investigation were : (1) To provide trustworthy data for the parachors and refractivities of a wide variety of pure liquid esters, (*a*) for the calculation of the contributions of the CO·O group, (*b*) as reference compounds in the computation of other atomic and structural constants, and (*c*) for their characterisation in qualitative organic analysis. (2) To test the validity of the assumption made by Eisenlohr and others that for esters the refractivities may be calculated from $[CH_2]_nO''O<$, *i.e.*, that the O_2 in carboxylic esters is the sum of the constants for the ketonic (O″) and ethereal oxygen (O <) atoms.

The values for the CO·O group in all the aliphatic esters investigated by the author are simply calculated by subtracting the figures for the corresponding hydrocarbons (Part IX, *J.*, 1946, 113) or, if this is not possible, the values for hydrogen and/or alkyl groups (Part XI, *loc. cit.*). It should be noted that the CH_2 figures, although accurately known (Part IX, *loc. cit.*), have not been widely employed in the calculations. The results are shown in Table I. The

TABLE I.

CO·O *Values from aliphatic esters.*

R =	*P.*	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.	R =	*P.*	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
Alkyl formates, H·CO_2R.													
Et	65·7	6·34	6·38	6·44	6·52	64·57	Am^i ‡ ...	65·2	6·40	6·44	6·50	6·57	64·66
Pr^n	65·8	6·39	6·42	6·49	6·56	64·62	$C_6H_{13}^n$...	66·5	6·51	6·54	6·61	6·68	64·69
Bu^n	65·5	6·44	6·48	6·54	6·61	64·61	Pr^i	68·9	6·56	6·58	6·65	6·72	64·12
Am^i † ...	65·4	6·35	6·38	6·46	6·53	64·63	Bu^t	67·0	6·55	6·58	6·65	6·72	64·52
Alkyl acetates, CH_3·CO_2R.													
Me	66·6	6·15	6·18	6·24	6·32	64·62	Bu^i	64·2	6·31	6·35	6·40	6·46	63·82
Et	64·4	6·25	6·29	6·35	6·42	64·05	Bu^s * ...	66·8	6·43	6·46	6·54	6·59	63·05
Pr^n	63·9	6·31	6·33	6·40	6·47	64·01	Am^n ...	64·0	6·31	6·34	6·41	6·47	64·06
Pr^i	64·8	6·30	6·33	6·40	6·46	63·58	Am^i † ...	63·9	6·28	6·31	6·36	6·44	63·98
Bu^n	63·7	6·23	6·25	6·32	6·38	63·96	$C_6H_{13}^n$...	63·6	6·29	6·31	6·38	6·42	64·18
Alkyl propionates, CH_3·CH_2·CO_2R.													
Me	63·6	6·14	6·19	6·24	6·30	64·45	Pr^n	62·1	6·14	6·16	6·21	6·28	63·85
Et	64·0	6·13	6·17	6·23	6·30	63·90	Bu^n	63·0	6·20	6·22	6·28	6·34	63·89
Alkyl *n*-butyrates, CH_3·CH_2·CH_2·CO_2R.													
Me	63·0	6·14	6·17	6·23	6·30	64·31	Bu^n	61·8	6·17	6·19	6·25	6·30	63·77
Et	62·0	6·19	6·20	6·27	6·33	63·74	Am^n ...	63·3	6·30	6·33	6·38	6·43	63·86
Pr^n	63·3	6·19	6·21	6·28	6·33	63·70	Am^i † ...	63·1	6·20	6·21	6·29	6·34	63·80
Alkyl *iso*butyrates, $(CH_3)_2$CH·CO_2R.													
Me	64·0	6·13	6·19	6·24	6·31	64·17	Pr^n	63·1	6·19	6·21	6·26	6·33	63·47
Et	63·3	6·18	6·20	6·26	6·32	63·43	Bu^n	63·0	6·21	6·23	6·28	6·34	63·49
Alkyl *n*-valerates, CH_3·$[CH_2]_3$·CO_2R.													
Me	62·6	6·14	6·16	6·23	6·29	64·29	Bu^n	62·2	6·15	6·19	6·24	6·28	63·81
Et	62·7	6·21	6·23	6·30	6·35	63·81	Am^n ...	61·4	6·19	6·22	6·27	6·30	63·73
Pr^n	61·6	6·15	6·17	6·24	6·28	63·82							

TABLE I—(*continued*).

R =	*P.*	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.	R =	*P.*	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
Alkyl *iso*valerates, $(CH_3)_2CH{\cdot}CH_2{\cdot}CO_2R$.													
Me	62·8	6·14	6·19	6·24	6·30	64·11	Pr^n	62·7	6·24	6·26	6·32	6·39	63·55
Et	62·3	6·22	6·25	6·32	6·37	63·50	Bu^n	62·3	6·19	6·22	6·28	6·33	63·56
Alkyl *n*-hexoates, $CH_3{\cdot}[CH_2]_4{\cdot}CO_2R$.													
Me	62·4	6·10	6·12	6·19	6·25	64·40	Et	61·4	6·14	6·16	6·23	6·26	63·89
Alkyl *n*-heptoates, $CH_3{\cdot}[CH_2]_5{\cdot}CO_2R$.													
Me	61·1	6·05	6·06	6·13	6·17	64·51	Et	62·6	6·13	6·16	6·21	6·26	63·94
Alkyl *n*-octoates, $CH_3{\cdot}[CH_2]_6CO_2R$.													
Me	63·7	6·10	6·13	6·18	6·23	64·60	Et	63·0	6·08	6·10	6·17	6·19	64·04
Alkyl *n*-decoates, $CH_3{\cdot}[CH_2]_8{\cdot}CO_2R$.													
Me	64·1	6·09	6·10	6·16	6·22	64·66	Pr^n	63·9	6·22	6·24	6·31	6·36	63·89
Et	63·3	6·11	6·15	6·21	6·26	64·05	Bu^n	63·2	6·10	6·14	6·20	6·25	63·90
Alkyl *n*-dodecoates, $CH_3{\cdot}[CH_2]_{10}{\cdot}CO_2R$.													
Me	65·4	6·15	6·16	6·23	6·29	64·72	Pr^n	61·7	6·07	6·10	6·15	6·19	63·97
Et	61·6	6·17	6·20	6·26	6·32	64·03	Bu^n	61·7	6·27	6·30	6·36	6·39	64·10
Dialkyl oxalates, $(CO_2R)_2$.													
Et	66·2	6·45	6·48	6·55	6·63	64·33	Bu^n	64·4	6·48	6·52	6·59	6·65	64·13
Pr^n	65·5	6·49	6·52	6·60	6·66	64·13	Am^n ...	64·0	6·44	6·47	6·54	6·60	64·09
Pr^i	69·0	6·82	6·85	6·93	7·00	64·11	Am^i † ...	64·0	6·47	6·50	6·58	6·63	64·13
Dialkyl malonates, $CH_2(CO_2R)_2$.													
Me	66·2	6·30	6·33	6·40	6·48	64·95	Et	64·9	6·28	6·31	6·38	6·45	64·20
Dialkyl succinates, $[CH_2]_2(CO_2R)_2$.													
Me	65·5	6·16	6·20	6·26	6·32	65·00	Bu^n	62·7	6·18	6·20	6·26	6·31	64·20
Et	63·8	6·17	6·19	6·25	6·31	64·42	Bu^i	61·7	6·25	6·28	6·33	6·38	64·16
Pr^n	62·9	6·21	6·24	6·30	6·36	64·32	Am^n ...	61·8	6·19	6·22	6·28	6·33	64·18
Pr^i	63·5	6·22	6·24	6·30	6·35	63·83	Am^i ‡ ...	63·1	6·21	6·25	6·31	6·35	64·30
Dialkyl glutarates, $[CH_2]_3(CO_2R)_2$.													
Me	64·8	6·06	6·08	6·14	6·22	65·02	Et	63·9	6·15	6·17	6·23	6·30	64·43
Dialkyl adipates, $[CH_2]_4(CO_2R)_2$.													
Me	65·6	6·12	6·14	6·20	6·25	65·16	Bu^n	63·3	6·16	6·19	6·26	6·29	64·31
Et	64·3	6·16	6·19	6·25	6·29	64·57	Am^n ...	62·3	6·12	6·15	6·21	6·25	64·27
Pr^n	64·2	6·14	6·16	6·22	6·27	64·39	Am^i † ...	62·8	6·11	6·13	6·20	6·24	64·43
Pr^i	64·2	6·17	6·20	6·25	6·29	64·00							
Dialkyl pimelates, $[CH_2]_5(CO_2R)_2$.													
Me	65·7	6·11	6·14	6·20	6·24	65·06	Et	64·9	6·16	6·19	6·24	6·31	64·42
Dialkyl suberates, $[CH_2]_6(CO_2R)_2$.													
Me	66·4	6·10	6·13	6·19	6·24	64·98	Pr^n	64·8	6·19	6·21	6·28	6·33	64·33
Et	65·8	6·18	6·21	6·27	6·37	64·46	Bu^n	62·8	6·12	6·13	6·21	6·24	64·25
Dialkyl sebacates, $[CH_2]_8(CO_2R)_2$.													
Et	66·1	6·20	6·23	6·29	6·34	64·48	Pr^n	64·6	6·11	6·13	6·19	6·23	64·30
							Mean CO·O	63·4	6·173	6·200	6·261	6·315	64·14

† With Bisol fermentation *iso*amyl alcohol.
‡ With Sharples synthetic *iso*amyl alcohol.

experimental figures for dialkyl malonates, glutarates, and pimelates are those of Part I (*J.*, 1934, 333). In the calculation of the mean values, the experimental data for alkyl formates, *sec.*-butyl acetate, dialkyl oxalates, and dialkyl malonates have been omitted; the individual variations are comparatively large and therefore there seems no valid reason for excluding the methyl esters from the computations. The high values for the dialkyl oxalates are doubtless due to some interaction between the two carboxyl groups (an effect which is apparent, but less marked, with the malonates): the subject will be discussed again in connexion with computations of bond refractivities. The mean values are:—

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
CO·O	63·4	6·173	6·200	6·261	6·315	64·14

These figures may be compared with those deduced from CO (Part XI, *loc. cit.*) + O in alkyl ethers (Part XII, preceding paper) :

CO	45·9	4·684	4·713	4·768	4·830	42·38
O (ethers)	19·8	1·753	1·764	1·786	1·805	22·74
CO + O (ethers)	65·7	6·437	6·477	6·554	6·635	65·12

It is evident that the constants for CO·O are not equal to the sum of those for CO (ketones) and O (alkyl ethers), and hence the assumption of Eisenlohr (*Z. physikal. Chem.*, 1910, **75**, 585) and others that

$$O_2 \text{ (esters)} = O'' \text{ (ketones)} + O< \text{ (ethers)}$$

has no experimental foundation. In view of the constancy of the values for CO·O and CO, it follows that the values for (CO·O − CO) will also be constant, but they are *not* the constants for ethereal oxygen O< as understood by Eisenlohr. To avoid ambiguity the author suggests that for calculations of the molecular refractivities of carboxylic esters, the figures for CO·O should be employed.

If the author's values for the constants of carbon (Part IX, *loc. cit.*) are subtracted from those for CO·O, the following figures are obtained for O_2 in carboxylic esters :

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
O_2 (esters)	54·8	3·601	3·609	3·660	3·660	38·43

Sugden (*J.*, 1924, **125**, 1177; "The Parachor and Valency", 1930, 42) gives *P* 60·0, whilst Eisenlohr's values (*loc. cit.*) for O'' + O< are R_C 3·828, R_D 3·854, R_F 3·896, and $R_{G'}$ 3·929, respectively.

TABLE II.

Comparison of $CH_3{\cdot}[CH_2]_n{\cdot}CH(CO_2R)_2$ and $[CH_2]_{n+2}(CO_2R)_2$.

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
$CH_3{\cdot}CH(CO_2Me)_2$	320·6	33·04	33·18	33·53	33·79	206·47
$(CH_3{\cdot}CO_2Me)_2$	321·7	32·84	32·99	33·34	33·59	207·45
$CH_3{\cdot}CH(CO_2Et)_2$	398·7	42·25	42·44	42·90	43·23	246·06
$(CH_3{\cdot}CO_2Et)_2$	398·5	42·12	42·30	42·75	43·08	247·32
$CH_3{\cdot}CH(CO_2Pr^n)_2$	476·3	51·57	51·79	52·34	52·74	287·02
$(CH_3{\cdot}CO_2Pr^n)_2$	476·2	51·42	51·65	52·20	52·62	288·24
$CH_3{\cdot}CH(CO_2Bu^n)_2$	553·8	60·89	61·02	61·68	62·15	328·20
$(CH_3{\cdot}CO_2Bu^n)_2$	555·3	60·63	60·89	61·55	62·01	329·30
$C_2H_5{\cdot}CH(CO_2Me)_2$	358·4	37·63	37·82	38·21	38·49	227·09
$[CH_2]_3(CO_2Me)_2$	361·4	37·27	37·43	37·83	38·16	228·01
$C_2H_5{\cdot}CH(CO_2Et)_2$	437·0	46·85	47·07	47·56	47·94	266·63
$[CH_2]_3(CO_2Et)_2$	439·6	46·73	46·93	47·43	47·83	267·89
$C_2H_5{\cdot}CH(CO_2Pr^n)_2$	515·1	56·17	56·44	57·02	57·47	307·64
$C_2H_5{\cdot}CH(CO_2Bu^n)_2$	592·0	65·31	65·62	66·30	66·82	348·72
$C_3H_7{}^n{\cdot}CH(CO_2Me)_2$	396·2	42·23	42·42	42·87	43·20	247·56
$[CH_2]_4(CO_2Me)_2$	402·0	42·02	42·20	42·65	42·97	248·80
$C_3H_7{}^n{\cdot}CH(CO_2Et)_2$	475·5	51·57	51·81	52·36	52·76	287·12
$[CH_2]_4(CO_2Et)_2$	479·1	51·31	51·54	52·09	52·47	288·74
$C_3H_7{}^n{\cdot}CH(CO_2Pr^n)_2$	555·3	60·81	61·08	61·73	62·21	328·22
$[CH_2]_4(CO_2Pr^n)_2$	558·2	60·55	60·82	61·48	61·93	329·68
$C_3H_7{}^n{\cdot}CH(CO_2Bu^n)_2$	630·7	69·99	70·30	71·06	71·60	369·24
$[CH_2]_4(CO_2Bu^n)_2$	636·6	69·77	70·09	70·84	71·35	370·81
$C_5H_{11}{}^n{\cdot}CH(CO_2Me)_2$	473·9	51·55	51·79	52·34	52·74	288·76
$[CH_2]_6(CO_2Me)_2$	483·3	51·19	51·42	51·97	52·37	289·57
$C_5H_{11}{}^n{\cdot}CH(CO_2Et)_2$	553·4	60·80	61·08	61·73	62·19	328·32
$[CH_2]_6(CO_2Et)_2$	561·4	60·64	60·91	61·56	62·13	329·83
$C_5H_{11}{}^n{\cdot}CH(CO_2Pr^n)_2$	631·8	70·06	70·37	71·12	71·68	369·40
$[CH_2]_6(CO_2Pr^n)_2$	639·6	69·82	70·13	70·87	71·43	370·84
$C_5H_{11}{}^n{\cdot}CH(CO_2Bu^n)_2$	709·0	79·32	79·67	80·52	81·15	410·33
$[CH_2]_6(CO_2Bu^n)_2$	717·0	79·02	79·36	80·21	80·82	411·99

Although it cannot be claimed that the purity of all the methyl and ethyl esters of the monobasic acids (particularly *n*-hexoic to *n*-dodecoic acid) is as high as that obtained for the normal aliphatic hydrocarbons (Part IX, *loc. cit.*), they do provide two homologous series (acetic acid

to *n*-dodecoic acid—*n*-nonoic and *n*-undecoic acids are absent) from which the CH_2 contributions may be calculated by the method of least squares. The results are :

CH_2 *from esters of monobasic acids,* $CH_3 \cdot [CH_2]_n \cdot CO_2R$.

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	Mn_D^{20}.
Methyl esters	39·87	4·623	4·638	4·698	4·721	20·62
Ethyl esters	39·75	4·619	4·640	4·688	4·725	20·61

These are in satisfactory agreement with the values found from other homologous series (compare Part IX).

Measurements have also been made upon esters of methyl-, ethyl-, *n*-propyl-, and *n*-amylmalonic acids. Apart from their own intrinsic merit and as reference compounds in the calculation of certain structural constants in subsequent papers of this series, the results are of importance in connexion with the deduction of bond refractivities of C–H in compounds of the type . The final results are collected in Table II.

Experimental.

Preparation of Esters.

Alkyl Formates.—A.R. (98/100%) Formic acid was used throughout, and the alcohols were of the highest purity (see Part VII, *J.*, 1943, 638) : *n*-propyl and the higher alcohols were purified, after drying ($CaSO_4$ or K_2CO_3), by fractional distillation. A mixture of the alcohol (1 mol.) and excess of formic acid (2 mols.) was refluxed for 24—30 hours and the ester was isolated by a procedure in which due regard was paid to its solubility in water.

Ethyl formate. A mixture of 61 g. of pure formic acid and 31 g. of absolute ethyl alcohol was refluxed on a steam-bath for 30 hours. It was then distilled from a flask with fractionating side arm until the temperature rose to 62°; the distillate was washed successively with saturated sodium chloride solution, saturated sodium hydrogen carbonate solution in the presence of solid sodium chloride, and dried ($MgSO_4$). Distillation gave 36 g. of ethyl formate, b. p. 53·5°/767 mm.

n-*Propyl formate.* A mixture of 46 g. of formic acid and 30 g. of *n*-propyl alcohol was refluxed for 22 hours and then fractionally distilled. The distillate, b. p. below 85°, was worked up as for ethyl formate and yielded 30 g. of ester, b. p. 81—82°/768 mm.

iso*Propyl formate.* A mixture of 46 g. of formic acid and 30 g. of *iso*propyl alcohol was refluxed for 22 hours. The excess of acid was removed by adding 10 ml. of saturated sodium hydrogen carbonate solution, followed by 15 g. of the solid salt in small portions; the lower layer was discarded, 10 ml. of saturated salt solution were added, and then solid sodium hydrogen carbonate until effervescence ceased. The ester was washed with saturated salt solution, dried, and distilled. The yield of *iso*propyl formate, b. p. 67·5—68°/767 mm., was 32 g.

n-*Butyl formate.* A mixture of 46 g. of formic acid and 37 g. of *n*-butyl alcohol was refluxed for 26 hours, then washed successively with saturated salt solution, saturated sodium hydrogen carbonate solution in the presence of saturated salt solution until effervescence ceased, saturated salt solution, and finally dried and distilled. The yield of ester, b. p. 105—107°/765 mm. (mainly 106·5°), was 40 g.

iso*Butyl formate.* A mixture of 46 g. of formic acid and 37 g. of *iso*butyl alcohol was refluxed for 26 hours and yielded, when worked up as for *n*-butyl formate, 45 g. of the ester, b. p. 96—98°/767 mm. (mainly 97·5°).

n-*Amyl formate.* A mixture of 46 g. of formic acid and 44 g. of *n*-amyl alcohol, after refluxing for 24 hours, yielded, after the usual procedure, 47 g. of ester, b. p. 130—131°/753 mm.

iso*Amyl formate.* The yield of ester from 46 g. of formic acid and 44 g. of *iso*amyl alcohol (Sharples synthetic), after refluxing for 18 hours, was 44 g. of b. p. 123—125°/763 mm. (mainly 124°). A similar preparation but with Bisol fermentation *iso*amyl alcohol gave 45 g. of b. p. 123—124°/761 mm.

n-*Hexyl formate.* A mixture of 46 g. of formic acid and 51 g. of *n*-hexyl alcohol was refluxed for 24 hours and yielded, when worked up as for *n*-butyl formate, 56 g. of ester, b. p. 153—154°/753 mm. (mainly 154°).

Alkyl Acetates.—A.R. Glacial acetic acid was used throughout and in large excess.

Methyl acetate. A mixture of 48 g. of absolute methyl alcohol, 270 g. of pure acetic acid, and 3 g. of concentrated sulphuric acid was refluxed for 5 hours. Upon fractionation of the reaction mixture, 112 g. of the crude ester passed over at 55—56° and the residual acid weighed 209 g.; the latter may be employed for the conversion of more methyl alcohol into the ester. The ester was washed successively with saturated salt solution, saturated sodium hydrogen carbonate solution until effervescence ceased, saturated salt solution, dried ($MgSO_4$), and distilled. The yield of pure methyl acetate, b. p. 56°/754 mm., was 92 g.

Ethyl acetate. A mixture of 58 g. of absolute ethyl alcohol, 225 g. of acetic acid, and 3 g. of concentrated sulphuric acid was refluxed for 12 hours. Water was added, the mixture saturated with sodium chloride to separate the ester layer, the latter was washed with saturated sodium hydrogen carbonate solution until neutral, then with saturated salt solution, and finally dried ($MgSO_4$). The yield of ethyl acetate, b. p. 76—77°/770 mm. (mainly 77°), was 32 g. An improved yield may be obtained by fractionating the crude reaction mixture as detailed for methyl acetate.

n-*Propyl acetate.* A mixture of 40 g. of *n*-propyl alcohol, 160 g. of glacial acetic acid, and 2 g. of concentrated sulphuric acid was refluxed for 12 hours. An equal weight of water was then added, and

the ester worked up as in the preceding preparation. The yield of *n*-propyl acetate, b. p. 101—102°/767 mm., was 36 g.

iso*Propyl acetate.* A mixture of 40 g. of *iso*propyl alcohol, 160 g. of acetic acid, and 2 g. of concentrated sulphuric acid was refluxed for 18 hours. After being worked up as above, the yield was 32 g.; b. p. 87—88°/759 mm.

n-*Butyl acetate.* Dry hydrogen chloride was passed into 37 g. of *n*-butyl alcohol until 1 g. was absorbed, 120 g. of acetic acid were added, and the mixture was refluxed for 8 hours. The reaction mixture was diluted with excess of water, and worked up as for ethyl acetate, but without the washing with saturated brine. The yield of *n*-butyl acetate, b. p. 125°/755 mm., was 40 g.

iso*Butyl acetate.* A mixture of 37 g. of *iso*butyl alcohol (containing 1 g. of dissolved hydrogen chloride) and 120 g. of acetic acid was refluxed for 11 hours. It was worked up as for *n*-butyl acetate and yielded 36 g. of ester, b. p. 115·5—116·5°/764 mm.

sec.-*Butyl acetate.* A mixture of 50 g. of *sec.*-butyl alcohol (containing 2·5 g. of dissolved hydrogen chloride) and 90 g. acetic acid was refluxed for 10 hours. It was worked up as for *n*-butyl acetate and afforded 35 g. of ester, b. p. 111—112°/765 mm.

tert.-*Butyl acetate.* This was prepared from 12 g. of magnesium, 37 g. of *tert.*-butyl alcohol, 100 ml. of anhydrous ether and a solution of 55 g. of pure acetyl chloride in 50 g. of anhydrous ether (see *Org. Synth.*, 1940, **20**, 21). The fractionation was conducted through a four-section, Pyrex, modified Young and Thomas column. The yield of ester, b. p. 96·5—98°/763 mm. (mainly 97·5°), was 49 g.

n-*Amyl acetate.* A mixture of 44 g. of *n*-amyl alcohol, 160 g. of acetic acid, and 2·5 g. of concentrated sulphuric acid was refluxed for 20 hours and yielded, when worked up as usual, 47 g. of ester, b. p. 147—148°/762 mm. (mainly 148°).

iso*Amyl acetate.* This was prepared exactly like the *n*-amyl ester except that 44 g. of Bisol fermentation *iso*amyl alcohol were used. The yield of ester, b. p. 141—142°/761 mm., was 46 g.

n-*Hexyl acetate.* A mixture of 34 g. of *n*-hexyl alcohol, 60 g. of acetic acid, and 1·7 g. of concentrated sulphuric acid was refluxed for 30 hours. It yielded, when worked up in the usual manner, 40 g. of ester, b. p. 167—170°/768 mm. (mainly 168—169°).

Alkyl Propionates.—The propionic acid (Boake Roberts) was carefully fractionated and the fraction of b. p. 141·5°/772 mm. was used. The " excess acid " method was employed throughout.

Methyl propionate. A mixture of 16 g. of absolute methyl alcohol, 111 g. of propionic acid, and 0·8 g. of concentrated sulphuric acid was refluxed for 24 hours and then distilled through an efficient column. The distillate (39 g.), b. p. 70—80°, was washed successively with saturated sodium hydrogen carbonate solution until neutral, then saturated salt solution, and dried, and distilled. The yield of ester, b. p. 79—80°/762 mm., was 31 g.

Ethyl propionate. A mixture of 23 g. of absolute ethyl alcohol, 111 g. of propionic acid, and 1·2 g. of concentrated sulphuric acid was refluxed for 24 hours. It was then fractionated and the portion distilling below 110° was collected as crude ester. This was purified as for methyl propionate and yielded 40 g. of ethyl propionate, b. p. 98—99°/763 mm.

n-*Propyl propionate.* A mixture of 30 g. of *n*-propyl alcohol, 111 g. of propionic acid, and 1·5 g. of concentrated sulphuric acid was refluxed for 24 hours, then poured into excess of water and worked up as usual. The yield of ester, b. p. 122—123°/767 mm., was 45 g.

n-*Butyl propionate.* A mixture of 37 g. of *n*-butyl alcohol, 111 g. of propionic acid, and 1·9 g. of concentrated sulphuric acid, refluxed for 24 hours, yielded, when worked up as usual, 55 g. of ester, b. p. 145·5°/767 mm.

Alkyl n-*Butyrates.*—The pure commercial acid (Boake Roberts) was carefully fractionated and the fraction of b. p. 163°/756 mm. used.

Methyl n-*butyrate.* A mixture of 44 g. of absolute methyl alcohol, 30 g. of *n*-butyric acid, and 6 ml. of concentrated sulphuric acid was refluxed for 14 hours. It was then poured into 300 ml. of water, the excess of acid neutralised with sodium hydrogen carbonate, and the ester extracted with ether and dried ($MgSO_4$). After removal of the ether, 18 g. of ester, b. p. 103°/774 mm., were obtained.

Ethyl n-*butyrate.* A mixture of 16 g. of absolute ethyl alcohol, 60 g. of *n*-butyric acid, and 4 ml. of concentrated sulphuric acid was refluxed for 14 hours. It was then poured into excess of water, washed with saturated sodium hydrogen carbonate solution until neutral and then with water, and dried and distilled. The yield of ethyl *n*-butyrate, b. p. 121°/771 mm., was 26 g.

n-*Propyl* n-*butyrate.* A mixture of 40 g. of *n*-propyl alcohol, 85 g. of *n*-butyric acid, and 6 ml. of concentrated sulphuric acid was refluxed for 24 hours, and the ester separated as for the ethyl compound. The yield of ester, b. p. 142—143°/767 mm., was 38 g.

n-Butyl n-*butyrate.* A mixture of 30 g. of *n*-butyl alcohol, 80 g. of *n*-butyric acid, and 6 ml. of concentrated sulphuric acid was refluxed for 25 hours. After being worked up as usual, 32 g. of ester, b. p. 164·5—165·5°/755 mm., were obtained.

n-*Amyl* n-*butyrate.* The yield of ester, b. p. 185—186°/757 mm., from a mixture of 27 g. of *n*-amyl alcohol, 60 g. of *n*-butryic acid, and 6 ml. of concentrated sulphuric acid refluxed for 28 hours, was 29 g.

iso*Amyl* n-*butyrate.* A mixture of 30 g. of *n*-butyric acid, 27 g. of *iso*amyl alcohol (Bisol fermentation), 70 ml. of sodium-dried A.R. benzene, and 6 ml. of concentrated sulphuric acid was refluxed for 27 hours. It was then poured into excess of water, the benzene layer separated and washed successively with water, saturated sodium hydrogen carbonate solution and water, and dried, and distilled. After the benzene had been removed, 42 g. of ester, b. p. 179·5°/780 mm., were collected.

Alkyl iso*Butyrates.*—Commercial *iso*butyric acid was distilled and the fraction, b. p. 154—154·5°/775 mm., collected.

Methyl iso*butyrate.* A mixture of 44 g. of *iso*butyric acid, 12 g. of absolute methyl alcohol, and 0·6 g. of concentrated sulphuric acid was refluxed for 26 hours and fractionally distilled. The distillate boiling below 110° (50 g.) was washed with saturated sodium hydrogen carbonate solution until neutral, then with saturated salt solution, and dried and distilled. The yield of ester, b. p. 91—92°/761 mm., was 30 g.

Ethyl iso*butyrate.* A mixture of 37 g. of *iso*butyric acid, 196 g. of absolute ethyl alcohol, and 10 g. of concentrated sulphuric acid was refluxed for 20 hours, the excess of alcohol distilled off on a water-bath

and the residue poured into excess of water. The upper layer of ester was separated and purified as usual. The yield of ester, b. p. 110°/762 mm., was 20 g.

n-*Propyl* iso*butyrate*. A mixture of 37 g. of *iso*butyric acid, 51·5 g. of *n*-propyl alcohol, 90 ml. of sodium-dried A.R. benzene, and 7 g. of concentrated sulphuric acid was refluxed for 31 hours, poured into excess of water, the benzene layer washed with saturated sodium hydrogen carbonate solution and water, and dried ($MgSO_4$). After removal of the benzene, 27 g. of ester, b. p. 133—134°/752 mm., were obtained upon fractionation.

n-*Butyl* iso*butyrate*. A mixture of 37 g. of *iso*butyric acid, 64 g. of *n*-butyl alcohol, 90 ml. of pure benzene, and 7 g. of concentrated sulphuric acid was refluxed for 31 hours. This was worked up as for the *n*-propyl ester and yielded 40 g. of ester, b. p. 155—156°/762 mm.

Alkyl n-*Valerates*.—The *n*-valeric acid, prepared by the hydrolysis of *n*-butyl cyanide, had b. p. 184°/767 mm.

Methyl n-*valerate*. A mixture of 46 g. of *n*-valeric acid, 8·6 g. of absolute methyl alcohol, and 0·5 g. of concentrated sulphuric acid was refluxed for 40 hours and then fractionally distilled until the b. p. reached 140°. The distillate consisted of two layers: the lower, aqueous layer was discarded, and the upper layer was washed with saturated sodium hydrogen carbonate solution until neutral and then with water, and dried and distilled. The yield of ester, b. p. 126°/750 mm., was 16 g.

Ethyl n-*valerate*. A mixture of 40 g. of *n*-valeric acid, 9 g. of absolute ethyl alcohol, and 0·5 g. of concentrated sulphuric acid was refluxed for 38 hours and then fractionally distilled until the temperature rose to 160°. The subsequent procedure was as given for the methyl ester and afforded 16 g. of ethyl *n*-valerate, b. p. 144°/762 mm.

n-*Propyl* n-*valerate*. A mixture of 25·5 g. of *n*-valeric acid, 30 g. of *n*-propyl alcohol, 50 ml. of sodium-dried A.R. benzene, and 10 g. of concentrated sulphuric acid was refluxed for 39 hours. This was poured into water, etc., and yielded 23 g. of ester, b. p. 162—164°/750 mm.

n-*Butyl* n-*valerate*. A mixture of 25·5 g. of *n*-valeric acid, 37 g. of *n*-butyl alcohol, 50 ml. of pure benzene, and 5 g. of concentrated sulphuric acid was refluxed for 53 hours. It was then poured into water, etc., and yielded 27 g. of ester, b. p. 183—185°/753 mm.

n-*Amyl* n-*valerate*. A mixture of 20·4 g. of *n*-valeric acid, 44 g. of *n*-amyl alcohol, 6 g. of concentrated sulphuric acid, and 60 ml. of pure benzene was refluxed for 21 hours and then poured into excess of water. The benzene layer was washed with saturated sodium hydrogen carbonate solution and water, dried ($MgSO_4$), and distilled. After the benzene had passed over, 19 g. of ester, b. p. 202—204°/749 mm. (mainly 202—202·5°), were obtained. This was redistilled and had b. p. 103°/23 mm.

Alkyl iso*Valerates*.—Kahlbaum's pure *iso*valeric acid was redistilled and the fraction, b. p. 176°/762 mm., collected.

Methyl iso*valerate*. A mixture of 51 g. of *iso*valeric acid, 12 g. of absolute methyl alcohol, and 0·6 g. of concentrated sulphuric acid was refluxed for 20 hours and then fractionally distilled until thetemperature rose to 135°. The distillate was washed successively with saturated sodium hydrogen carbonate solution and saturated salt solution, dried, and distilled. The yield of ester, b. p. 115—116°/760 mm., was 26 g.

Ethyl iso*valerate*. A mixture of 51 g. of *iso*valeric acid, 11 g. of absolute ethyl alcohol, and 1 g. of concentrated sulphuric acid was refluxed for 20 hours, and then fractionally distilled until the temperature rose to 155°. After the usual procedure, the yield of ester, b. p. 132·5—134°/777 mm., was 24 g.

n-*Propyl* iso*valerate*. A mixture of 34 g. of *iso*valeric acid, 40 g. of *n*-propyl alcohol, 67 ml. of pure benzene, and 13·5 g. of concentrated sulphuric acid was refluxed for 30 hours, and then poured into water. The ester was isolated as usual. The yield was 38 g., b. p. 156—156·5°/755 mm.

n-*Butyl* iso*valerate*. A mixture of 34 g. of *iso*valeric acid, 49 g. of *n*-butyl alcohol, 67 ml. of pure benzene, and 13·5 g. of concentrated sulphuric acid was refluxed for 30 hours, and worked up as usual. The yield of ester, b. p. 175—176°/755 mm., was 42 g.

Alkyl n-*Hexoates* (n-*Caproates*).—Commercial *n*-hexoic acid (Carbon and Carbide Corporation) was fractionated, and the portion of b. p. 202—203°/768 mm. collected.

Methyl n-*hexoate*. A mixture of 58 g. of *n*-hexoic acid, 10·7 g. of absolute methyl alcohol, and 0·5 g. of concentrated sulphuric acid was refluxed for 30 hours and then fractionally distilled until the temperature rose to 155° (most passed over at 145—155°). The lower layer of the distillate was discarded, the ester washed with saturated sodium hydrogen carbonate solution and water, then dried and distilled. The yield of ester, b. p. 148—150°/760 mm., was 35 g.

Ethyl n-*hexoate*. A mixture of 58 g. of *n*-hexoic acid, 11·5 g. of absolute ethyl alcohol, and 0·6 g. of concentrated sulphuric acid was refluxed for 40 hours and then fractionally distilled until the temperature rose to 175°. The aqueous layer of the distillate was discarded and, after purification, 28 g. of the ester, b. p. 163·5—165·5°/752 mm., were isolated.

Alkyl n-*Heptoates*.—Pure commercial œnanthic acid (B.D.H.) was fractionated, and the fraction of b. p. 220—222°/768 mm. collected.

Methyl n-*heptoate*. A mixture of 35 g. of *n*-heptoic acid, 86 g. of absolute methyl alcohol, and 4·3 g. of concentrated sulphuric acid was refluxed for 12 hours, then poured into a large excess of water, and the ester layer separated and purified. The yield of ester, b. p. 170—173°/761 mm., was 35 g.

Ethyl n-*heptoate*. A mixture of 35 g. of *n*-heptoic acid, 134 g. of absolute ethyl alcohol, and 6·2 g. of concentrated sulphuric acid was refluxed for 12 hours and yielded, as for the methyl ester, 38 g. of ethyl *n*-heptoate, b. p. 184—186·5°/764 mm.

Alkyl n-*Octoates*.—Commercial pure *n*-octoic acid (Deutsche Hydrierwerke) was distilled, and the portion of b. p. 235—239°/762 mm. collected.

Methyl n-*octoate*. The yield of ester from 36 g. of *n*-octoic acid, 80 g. of absolute methyl alcohol, and 4 g. of concentrated sulphuric acid after refluxing for 12 hours was 33 g. of b. p. 191—192°/759 mm.

Ethyl n-*octoate*. The yield from 36 g. of *n*-octoic acid, 115 g. of absolute ethyl alcohol, and 6 g. of concentrated sulphuric acid after refluxing for 30 hours was 33 g. of b. p. 205—208°/742 mm.

Alkyl n-*Decoates*.—Commercially pure capric acid (Deutsche Hydrierwerke), m. p. 31—32°, was used.

Methyl n-*decoate*. The yield of ester from 43 g. of *n*-decoic acid, 80 g. of absolute methyl alcohol, and 4 g. of concentrated sulphuric acid, after refluxing for 25 hours, was 39 g. of b. p. 227—229°/758 mm.

Ethyl n-*decoate.* The yield of ester from 43 g. of decoic acid, 115 g. of absolute ethyl alcohol, and 6 g. of concentrated sulphuric acid, after refluxing for 22 hours, was 41 g. of b. p. 241—242·5°/760 mm.

n-*Propyl* n-*decoate.* The yield of *ester* from 34·5 g. of capric acid, 24 g. of *n*-propyl alcohol, 40 ml. of pure benzene, and 8 g. of concentrated sulphuric acid, after refluxing for 12 hours, was 39 g. of b. p. 114—115°/4·5 mm. (Found: C, 73·0; H, 11·9. $C_{13}H_{26}O_2$ requires C, 72·8; H, 12·2%).

n-*Butyl* n-*decoate.* The yield of *ester* from 34·5 g. of *n*-decoic acid, 30 g. of *n*-butyl alcohol, 40 ml. of pure benzene, and 8 g. of concentrated sulphuric acid, after refluxing for 12 hours, was 40 g. of b. p. 122—124°/4 mm. (Found: C, 73·6; H, 12·3. $C_{14}H_{28}O_2$ requires C, 73·6; H, 12·4%).

Alkyl n-*Docecoates.*—Commercially pure lauric acid (Deutsche Hydrierwerke), m. p. 45—46, was used.

Methyl n-*dodecoate.* The yield of ester from 40 g. of lauric acid, 64 g. of absolute methyl alcohol, and 3·5 g. of concentrated sulphuric acid, after refluxing for 18 hours, was 35 g. of b. p. 261—263°/766 mm.

Ethyl n-*dodecoate.* The yield of ester from 40 g. of lauric acid, 92 g. of absolute ethyl alcohol, and 4·6 g. of concentrated sulphuric acid, after refluxing for 20 hours, was 39 g. of b. p. 272—274°/764 mm.

n-*Propyl* n-*dodecoate.* The yield of *ester* from 33 g. of lauric acid, 20 g. of *n*-propyl alcohol, 35 ml. of pure benzene, and 6·5 g. of concentrated sulphuric acid, after refluxing for 38 hours, was 35 g. of b. p. 139—140°/4 mm. (Found: C, 74·3; H, 12·3. $C_{15}H_{30}O_2$ requires C, 74·3; H, 12·5%).

n-*Butyl* n-*dodecoate.* The yield of *ester* from 33 g. of the acid, 25 g. of *n*-butyl alcohol, 35 ml. of pure benzene, and 6·5 g. of concentrated sulphuric acid, after refluxing for 38 hours, was 40 g. of b. p. 152—153·5°/4·5 mm. (Found: C, 75·0; H, 12·3. $C_{16}H_{32}O_2$ requires C, 74·9; H, 12·6%).

Dialkyl Oxalates.—A.R. Oxalic acid dihydrate was dehydrated by heating the finely-powdered acid, spread upon large clock-glasses, in an electrically-heated oven at 105° for 6 hours, and then allowing it to cool in a desiccator. The loss in weight was theoretical.

The general method of preparation consisted in refluxing a mixture of 1 mol. of acid, 2·5—3·5 mols. of the alcohol, sodium-dried A.R. benzene (twice the volume of alcohol), and concentrated sulphuric acid for 6—12 hours, pouring the reaction mixture into a large excess of water, and separating the benzene layer; the aqueous extract phase was extracted with ether, and the extract combined with the benzene layer. The combined extracts were washed with saturated sodium hydrogen carbonate solution until free from acid, then with water, dried ($MgSO_4$), and distilled: the benzene passed over first, followed by the oxalate. The quantities used and the yields and b. p.s obtained are tabulated below.

Oxalate.	Acid, g.	Alcohol, g.	C_6H_6, ml.	H_2SO_4 (conc.), g.	Refluxing period (hrs.).	B. p.	Yield, g.
Ethyl	37	67	125	24	24	182—183°/764 mm.	47
n-Propyl	37	87	125	27	34	211—212/749 mm.	59
*iso*Propyl	37	87	125	27	23	188—191/757 mm.	57
n-Butyl	37	108	125	27	20	242—245/773 mm.	59
n-Amyl	18·5	64	63	13·5	32	138—139/9 mm.	34
*iso*Amyl †.....	18·5	64	63	13·5	22	127—128/7 mm.	40

Dialkyl Succinates.—A.R. Succinic acid, m. p. 185°, was used throughout.

Succinate.	Acid, g.	Alcohol, g.	C_6H_6, ml.	H_2SO_4 (conc.), g.	Refluxing period (hrs.).	B. p.	Yield, g.
Methyl	20	32	80	14	5	195/756 mm.	17·5
Ethyl	40	46	120	14	8	81/3 mm.	47
n-Propyl	30	45	110	11	12	101·5/3 mm.	37·5
*iso*Propyl	30	45	120	14	12	82/3 mm.	34
n-Butyl	30	54	140	14	20	121/3 mm.	45
*iso*Butyl	30	75	100	2	28	116/4 mm.	39
n-Amyl	30	90	220	18	22	129/2 mm.	58
*iso*Amyl ‡	30	90	220	21	14	130/4 mm.	57
*iso*Amyl †	20	45	60	8	32	150/9 mm.	38

Dialkyl Adipates.—Commercially pure adipic acid was crystallised from acetone and dried in a vacuum desiccator; m. p. 152·5°.

Adipate.	Acid, g.	Alcohol, g.	C_6H_6, ml.	H_2SO_4 (conc.), g.	Refluxing period (hrs.).	B. p.	Yield, g.
Methyl	40	40	100	14	6	120—121°/17 mm.	42
Ethyl	30	38	80	12	15	134·5/17 mm.	40
n-Propyl	30	39	75	12	14	145—146/9 mm.	40
*iso*Propyl	30	39	75	12	12	120—121/6—7 mm.	32
n-Butyl	40	66	100	16	26	158—159/7 mm.	56
n-Amyl	30	57	75	12	27	185—186/10 mm.	46
*iso*Amyl	30	57	75	12	23	184—185/13 mm.	42

Dialkyl Suberates.—The suberic acid had m. p. 140° and was prepared from castor oil (compare Vogel, *J.*, 1928, 2033).

Suberate.	Acid, g.	Alcohol, g.	C_6H_6, ml.	H_2SO_4 (conc.), g.	Refluxing period (hrs.).	B. p.	Yield, g.
Methyl	29	20	65	10	33	120°/6 mm.	30
Ethyl	29	23	65	10	33	131/5 mm.	23
n-*Propyl* [1]	29	30	65	10	38	164—165/8 mm.	36
n-*Butyl* [2]	29	37	65	10	31	175—176/4·5 mm.	40

[1] Found: C, 64·9; H, 9·9. $C_{14}H_{26}O_4$ requires C, 65·1; H, 10·1%.
[2] Found: C, 66·9; H, 10·4. $C_{16}H_{30}O_4$ requires C, 67·1; H, 10·6%.

Dialkyl Sebacates.—Schuchardt's pure acid was recrystallised from acetone and had m. p. 133—134°.

Sebacate.	Acid, g.	Alcohol, g.	C_6H_6, ml.	H_2SO_4 (conc.), g.	Refluxing period (hrs.).	B. p.	Yield, g.
Ethyl	34	23	65	10	36	156°/6 mm.	38
n-*Propyl* [3]	34	23	65	10	28	178—179/5 mm.	40

[3] Found: C, 66·8; H, 10·3. $C_{16}H_{30}O_4$ requires C, 67·1; H, 10·6%.

Dialkyl Methylmalonates.—Although methylmalonamide, m. p. 207°, can be readily prepared, the isolation of pure methylmalonic acid is a long and tedious process (Meyer and Bock, *Annalen*, 1896, **347**, 93). To prepare the pure esters, the method adopted was the hydrolysis of the pure amide, followed by conversion of the resulting solution of the sodium salt into the insoluble silver salt: the latter was then treated with the appropriate alkyl halide.

Crude diethyl methylmalonate, b. p. 193—195°/768 mm. (Meyer and Bock, *loc. cit.*), was shaken mechanically with 3 times its weight of concentrated ammonia solution for 12 hours and the resulting crude amide was recrystallised from 70% ethyl alcohol to constant m. p. (207°). 67 G. of the pure amide were heated under reflux with a solution of 54 g. of A.R. sodium hydroxide in 250 ml. of water until the evolution of ammonia ceased, the solution was then cautiously acidified with dilute nitric acid and then neutralised with concentrated ammonia solution to nitrazine-yellow indicator, and the precipitated silica filtered off. The filtrate was diluted somewhat, and a solution of 170 g. of silver nitrate in 200 ml. of water was added with stirring. The precipitate was collected after 12 hours, washed, and dried at 50—70°. The yield of silver methylmalonate was 185 g.

Dimethyl methylmalonate. A mixture of 47 g. of dry silver methylmalonate, 41 g. of pure colourless methyl iodide, and 100 ml. of sodium-dried ether was refluxed for 11 hours, the ether decanted, and the solid extracted with four 25-ml. portions of ether. After removal of the ether from the combined extracts, 15·5 g. of ester, b. p. 176—177°/761 mm., were obtained.

Diethyl methylmalonate. A mixture of 41·5 g. of silver methylmalonate, 40 g. of pure colourless ethyl iodide, and 75 ml. of sodium-dried A.R. benzene was refluxed for 8 hours. The mixture was filtered, and the solid was washed with three 40-ml. portions of pure benzene. The combined benzene extracts were washed successively with saturated sodium hydrogen carbonate solution (to remove traces of acid) and water, and dried, and distillled. The yield of ester, b. p. 195—196°/775 mm., was 13 g.

Di-n-propyl methylmalonate. A mixture of 41·5 g. of silver methylmalonate, 45 g. of pure colourless *n*-propyl iodide, and 75 ml. of pure, dry benzene was refluxed for 10 hours and yielded (details as for the ethyl ester) 15 g. of the *ester*, b. p. 225—226°/771 mm. (Found: C, 59·3; H, 8·9. $C_{10}H_{18}O_4$ requires C, 59·4; H, 9·0%).

Di-n-butyl methylmalonate. A mixture of 41·5 g. of silver methylmalonate, 46 g. of pure colourless *n*-butyl iodide, and 75 ml. of pure, dry benzene, refluxed for 14 hours, afforded (details as for the ethyl ester) 18 g. of the *ester*, b. p. 254—256°/761 mm. (Found: C, 62·5; H, 9·8. $C_{12}H_{22}O_4$ requires C, 62·6; H, 9·6%).

Dialkyl Ethylmalonates.—Ethylmalonic acid was prepared in the usual manner from ethyl sodiomalonate and ethyl iodide, followed by hydrolysis of the resulting diethyl ethylmalonate with aqueous-alcoholic potassium hydroxide; upon recrystallisation from benzene–ether–light petroleum (b. p. 40—60°), it had m. p. 110—111°.

The esters were prepared by the alcohol–benzene–sulphuric acid method. The experimental details are summarised below.

Ethyl-malonate.	Acid, g.	Alcohol, g.	C_6H_6, ml.	H_2SO_4 (conc.), g.	Refluxing period (hrs.).	B. p.	Yield, g.
Methyl	39·6	40	120	18	22	190°/761 mm.; 85°/15 mm.	24
Ethyl	19·8	28	60	9	19	109/24 mm.	21
n-*Propyl* [4]	19·8	42	60	9	20	123/15 mm.	23
n-*Butyl* [5]	19·8	55	60	9	20	145/14 mm.	25

[4] Found: C, 60·8; H, 9·2. $C_{11}H_{20}O_4$ requires C, 61·1; H, 9·3%.
[5] Found: C, 64·0; H, 9·9. $C_{13}H_{24}O_4$ requires C, 63·9; H, 9·9%.

Dialkyl n-*Propylmalonates.*—*n*-Propylmalonic acid was prepared as follows. To a solution of 34·5 g. of sodium in 345 g. of absolute ethyl alcohol were added 240 g. of dry diethyl malonate; after 2 hours 185 g. of *n*-propyl bromide were introduced during 90 minutes. The mixture was refluxed until neutral (2—3 hours), most of the alcohol was distilled off on a water-bath, the residue diluted with water, the ester layer separated, and the aqueous layer extracted with ether. The ester and extracts were dried ($MgSO_4$) and distilled; the yield of diethyl *n*-propylmalonate, b. p. 219—226°/775 mm. (mainly 220—222°), was 220 g. 156 G. of pure potassium hydroxide were dissolved in 156 g. of water, rectified spirit (500 ml.) was added until a homogeneous solution resulted, and the 220 g. of ester were introduced. The mixture was refluxed until a test portion dissolved completely in water (3 hours), and the alcohol was distilled off from a water-bath. The residue was dissolved in water, cooled to 0°, and dilute sulphuric acid was added slowly with vigorous stirring until the solution was acid to Congo-red. The acid was separated by three extractions with ether, the extracts dried, and the solvent removed on a water-bath. The syrupy residue was spread in thin layers upon large clock-glasses and largely crystallised when left overnight; the acid was collected on a sintered-glass funnel and washed with a little light petroleum (b. p. 40—60°); the *n*-propylmalonic acid (39 g.) had m. p. 95—96° after drying on a porous tile. The filtrate was spread on large clock-glasses, and the process repeated. The total yield of pure acid, m. p. 95—96° (*ex* benzene), was 115 g.

The experimental data relating to the preparation of the esters are summarised below.

n-Propylmalonate.	Acid, g.	Alcohol, g.	C_6H_6, ml.	H_2SO_4 (conc.), g.	Refluxing period (hrs.).	B. p.	Yield, g.
Methyl [6]	20·5	18·5	55	9	38	203—204°/760 mm.	18·5
Ethyl	18·5	23·5	50	8	38	221—222/767 mm.	18
n-*Propyl* [7]	20·5	36	55	8·5	30	120—121/6 mm.	25
n-*Butyl* [8]	20·5	42	55	8·5	35	150/9 mm.	32

[6] Found: C, 55·0; H, 8·1. $C_8H_{14}O_4$ requires C, 55·2; H, 8·1%.
[7] Found: C, 62·3; H, 9·5. $C_{12}H_{22}O_4$ requires C, 62·6; H, 9·6%.
[8] Found: C, 65·3; H, 10·4. $C_{14}H_{26}O_4$ requires C, 65·1; H, 10·2%.

Dialkyl n-*Amylmalonates.*—*n*-Amylmalonic acid was prepared similarly to *n*-propylmalonic acid except that crystallisation of the crude acid was achieved by leaving it in a vacuum desiccator over anhydrous calcium chloride and silica gel. Recrystallisation from benzene gave the pure acid, m. p. 82°. The experimental data for the preparation of the esters are summarised in the following table.

n-Amylmalonate.	Acid, g.	Alcohol, g.	C_6H_6, ml.	H_2SO_4 (conc.), g.	Refluxing period (hrs.).	B. p.	Yield, g.
Methyl [9]	25	18·5	55	8·5	18	104°/4·5 mm.	25
Ethyl [10]	25	26·5	55	8·5	26	113/3·5 mm.	28·5
n-*Propyl* [11]	20	28	45	7·5	28	136/4 mm.	25·5
n-*Butyl* [12]	20	34	45	7·5	34	152—152·5/3·5 mm.	29

[9] Found: C, 59·4; H, 8·8. $C_{10}H_{18}O_4$ requires C, 59·4; H, 9·0%.
[10] Found: C, 62·8; H, 9·6. $C_{13}H_{22}O_4$ requires C, 62·6; H, 9·6%.
[11] Found: C, 65·2; H, 10·0. $C_{14}H_{26}O_4$ requires C, 65·1; H, 10·1%.
[12] Found: C, 67·2; H, 10·5. $C_{16}H_{30}O_4$ requires C, 67·1; H, 10·6%.

Physical Measurements.—The above esters were redistilled immediately before use and a middle fraction was employed in the measurements.

180. *Ethyl formate.* B. p. 53·5°/767 mm.; M 74·08; n_C 1·35799, n_D 1·35983, n_F 1·36425, $n_{G'}$ 1·36735; R_C 17·63, R_D 17·71, R_F 17·90; $R_{G'}$ 18·04; $Mn_{4^\circ}^{20^\circ}$ 100·73. Densities determined: $d_{4^\circ}^{20^\circ}$ 0·9229, $d_{4^\circ}^{40\cdot2^\circ}$ 0·8985. Apparatus *A*.

(These headings apply to corresponding columns in all the following tables.)

t.	H.	$d_{4^\circ}^{t^\circ}$.	γ.	P.	t.	H.	$d_{4^\circ}^{t^\circ}$.	γ.	P.
22·9°	13·68	0·9218	23·56	177·3	41·4°	12·52	0·8971	21·03	177·3
22·7	13·58	0·9197	23·39	177·2				Mean	177·3

181. n-*Propyl formate.* B. p. 81·5°/768 mm.; M 88·10; n_C 1·37492, n_D 1·37693; n_F 1·38159, $n_{G'}$ 1·38494; R_C 22·31, R_D 22·41, R_F 22·66, $R_{G'}$ 22·84; $Mn_{4^\circ}^{20^\circ}$ 121·31. Densities determined: $d_{4^\circ}^{20^\circ}$ 0·9039, $d_{4^\circ}^{41\cdot6^\circ}$ 0·8812, $d_{4^\circ}^{60\cdot0^\circ}$ 0·8602. Apparatus *A*.

26·1°	14·18	0·8973	23·83	216·9	41·5°	13·36	0·8812	22·04	216·8
33·2	13·87	0·8907	23·13	217·0	61·2	12·40	0·8589	19·94	217·2
								Mean	217·0

182. n-*Butyl formate.* B. p. 106·5°/765 mm.; M 102·13; n_C 1·38706, n_D 1·38903, n_F 1·39383, $n_{G'}$ 1·39727; R_C 26·97, R_D 27·09, R_F 27·38, $R_{G'}$ 27·60; $Mn_D^{20^\circ}$ 141·86. Densities determined: $d_{4^\circ}^{20^\circ}$ 0·8917, $d_{4^\circ}^{41\cdot7^\circ}$ 0·8701, $d_{4^\circ}^{61\cdot8^\circ}$ 0·8492, $d_{4^\circ}^{80\cdot5^\circ}$ 0·8231. Apparatus *D*.

21·3°	11·32	0·8904	24·89	256·2	61·9°	9·88	0·8491	20·72	256·6
41·3	10·64	0·8705	22·87	256·6	86·7	8·95	0·8219	18·17	256·6
								Mean	256·5

183. n-*Amyl formate.* B. p. 130·5°/753 mm.; M 116·16; n_C 1·39768, n_D 1·39974, n_F 1·40469, $n_{G'}$ 1·40829; R_C 31·67, R_D 31·81, R_F 32·16, $R_{G'}$ 32·41; $Mn_D^{20^\circ}$ 162·59. Densities determined: $d_{4^\circ}^{20^\circ}$ 0·8846, $d_{4^\circ}^{42\cdot0^\circ}$ 0·8644, $d_{4^\circ}^{60\cdot9^\circ}$ 0·8463, $d_{4^\circ}^{80\cdot6^\circ}$ 0·8208. Apparatus *D*.

24·8°	11·78	0·8801	25·60	296·9	60·7°	10·45	0·8465	21·85	296·7
30·3	11·56	0·8749	24·98	296·8	86·7	9·50	0·8207	19·25	296·5
42·1	11·13	0·8643	23·76	296·7				Mean	296·7

184. n-*Hexyl formate.* B. p. 154°/753 mm.; M 130·18; n_C 1·40499, n_D 1·40706, n_F 1·41214, $n_{G'}$ 1·41576; R_C 36·30, R_D 36·47, R_F 36·86, $R_{G'}$ 37·15; $Mn_D^{20^\circ}$ 183·18. Densities determined: $d_{4^\circ}^{20^\circ}$ 0·8789, $d_{4^\circ}^{41\cdot6^\circ}$ 0·8609, $d_{4^\circ}^{60\cdot4^\circ}$ 0·8440, $d_{4^\circ}^{80\cdot5^\circ}$ 0·8218. Apparatus *D*.

22·8°	12·31	0·8765	26·65	337·4	61·1°	10·97	0·8434	22·85	337·5
27·7	12·13	0·8723	26·13	337·4	86·4	10·11	0·8209	20·50	337·4
40·9	11·62	0·8614	24·72	337·1				Mean	337·4

185. iso*Propyl formate.* B. p. 67·5—68°/767 mm.; M 88·10; n_C 1·36588, n_D 1·36783, n_F 1·37232, $n_{G'}$ 1·37561; R_C 22·49, R_D 22·59, R_F 22·84, $R_{G'}$ 23·02; $Mn_D^{20°}$ 120·51. Densities determined: $d_4^{20°}$ 0·8774, $d_4^{40·2°}$ 0·8541. Apparatus *D*.

t.	*H.*	$d_{4°}^{t°}$	γ.	*P.*	*t.*	*H.*	$d_{4°}^{t°}$	γ.	*P.*
18·7°	10·34	0·8789	22·44	218·3	40·3°	9·46	0·8540	19·95	218·6
25·3	10·05	0·8713	21·63	218·2				Mean	218·4

186. iso*Butyl formate.* B. p. 97·5°/767 mm.; M 102·13; n_C 1·38352, n_D 1·38546, n_F 1·39025, $n_{G'}$ 1·39372; R_C 27·11, R_D 27·23, R_F 27·53, $R_{G'}$ 27·75; $Mn_D^{20°}$ 141·50. Densities determined: $d_4^{20°}$ 0·8798, $d_4^{40·5°}$ 0·8588, $d_4^{59·3°}$ 0·8386. Apparatus *D*.

15·4°	11·20	0·8846	24·47	256·8	40·2°	10·17	0·8591	21·58	256·3
18·7	11·02	0·8811	23·98	256·5	59·6	9·41	0·8383	19·48	256·3
22·3	10·92	0·8775	23·66	256·7				Mean	256·5

187A. iso*Amyl formate* (from Bisol fermentation alcohol). B. p. 123·5°/761 mm.; n_C 1·39497, n_D 1·39700, n_F 1·40191, $n_{G'}$ 1·40546; R_C 31·55, R_D 31·69, R_F 32·04, $R_{G'}$ 32·29; $Mn_D^{20°}$ 162·28. Densities determined: $d_4^{20°}$ 0·8827, $d_4^{40·4°}$ 0·8629, $d_4^{61·8°}$ 0·8417, $d_4^{85·7°}$ 0·8175. Apparatus *D*.

16·9°	11·54	0·8858	25·24	293·9	61·1°	9·92	0·8424	20·64	294·1
41·3	10·67	0·8620	22·71	294·2	87·8	8·95	0·8154	18·02	294·4
								Mean	294·2

187B. iso*Amyl formate* (from Sharples synthetic alcohol). B. p. 124°/763 mm.; M 116·16; n_C 1·39606, n_D 1·39807, n_F 1·40298, $n_{G'}$ 1·40659; R_C 31·52, R_D 31·66, R_F 32·00, $R_{G'}$ 32·26; $Mn_D^{20°}$ 162·40. Densities determined: $d_4^{20°}$ 0·8857, $d_4^{39·4°}$ 0·8662, $d_4^{59·7°}$ 0·8465, $d_4^{85·4°}$ 0·8207. Apparatus *A*.

17·2°	15·20	0·8885	25·29	293·2	61·5°	13·12	0·8447	20·75	293·7
23·3	14·91	0·8824	24·64	293·3	87·2	11·86	0·8189	18·19	293·4
40·8	14·15	0·8648	22·91	293·9				Mean	293·5

188. *Methyl acetate.* B. p. 56°/754 mm.; M 74·08, n_C 1·36015, n_D 1·36193, n_F 1·36629, $n_{G'}$ 1·36930; R_C 17·42, R_D 17·49, R_F 17·68, $R_{G'}$ 17·81; $Mn_D^{20°}$ 100·89. Densities determined: $d_4^{20°}$ 0·9390, $d_4^{40·9°}$ 0·9125. Apparatus *D*.

21·0°	10·87	0·9377	25·17	177·1	41·0°	10·04	0·9124	22·62	177·4
25·7	10·76	0·9318	24·76	177·4				Mean	177·3

A Bisol sample of methyl acetate was purified by washing with saturated potassium carbonate solution, and water, and the ester was salted out with A.R. sodium chloride, dried with A.R. anhydrous potassium carbonate, and distilled through a three-section, Pyrex Young and Thomas column; it had b. p. 56·5°/758 mm., $d_4^{20°}$ 0·9315, $n_D^{20°}$ 1·36189; the low density would appear to indicate the presence of impurities not removable by fractionation.

189. *Ethyl acetate.* B. p. 77°/770 mm.; M 88·10; n_C 1·37050, n_D 1·37233, n_F 1·37683, $n_{G'}$ 1·37993; R_C 22·15, R_D 22·24, R_F 22·48, $R_{G'}$ 22·65; $Mn_D^{20°}$ 120·90. Densities determined: $d_4^{20°}$ 0·9009, $d_4^{42·0°}$ 0·8747, $d_4^{59·0°}$ 0·8533. Apparatus *D*.

20·3°	10·68	0·9005	23·75	216·0	42·6°	9·76	0·8740	21·07	216·2
29·1	10·41	0·8899	22·87	216·5	61·4	8·95	0·8504	18·80	216·2
								Mean	216·2

190. n-*Propyl acetate.* B. p. 101·5°/767 mm.; M 102·13; n_C 1·38249, n_D 1·38442, n_F 1·38899, n_G 1·39230; R_C 26·84, R_D 26·95, R_F 27·24, $R_{G'}$ 27·45; $Mn_D^{20°}$ 141·39. Densities determined: $d_4^{20°}$ 0·8867, $d_4^{41·5°}$ 0·8658, $d_4^{61·6°}$ 0·8432, $d_4^{87·0°}$ 0·8150. Apparatus *A*.

22·1°	14·55	0·8845	24·13	255·8	62·0°	12·40	0·8428	19·57	255·2
41·1	13·58	0·8662	22·03	255·4	87·3	11·06	0·8147	16·87	254·7
								Mean	255·3

191. iso*Propyl acetate.* B. p. 88°/759 mm.; M 102·13; n_C 1·37542, n_D 1·37730, n_F 138187, $n_{G'}$ 1·38507; R_C 26·84, R_D 26·96, R_F 27·26, $R_{G'}$ 27·46; $Mn_D^{20°}$ 140·66. Densities determined: $d_4^{20°}$ 0·8718, $d_4^{41·7°}$ 0·8502, $d_4^{62·1°}$ 0·8251. Apparatus *D*.

21·0°	10·32	0·8708	22·14	254·4	41·4°	9·56	0·8505	20·08	254·4
22·0	10·29	0·8697	22·10	254·6	61·1	8·75	0·8262	17·85	254·5
								Mean	254·5

192. n-*Butyl acetate.* B. p. 125°/755 mm.; M 116·16; n_C 139208, n_D 1·39406, n_F 1·39881, $n_{G'}$ 1·40228; R_C 31·39, R_D 31·53, R_F 31·87, $R_{G'}$ 32·11; $Mn_D^{20°}$ 161·94. Densities determined: $d_D^{20°}$ 0·8813, $d_4^{41·0°}$ 0·8630, $d_4^{60·5°}$ 0·8431, $d_4^{84·5°}$ 0·8177. Apparatus *A*.

20·9°	15·29	0·8804	25·21	295·6	60·8°	13·30	0·8426	20·99	295·1
29·3	15·01	0·8726	24·53	296·2	86·4	12·00	0·8159	18·33	295·0
41·0	14·38	0·8630	23·24	295·5				Mean	295·5

193. iso*Butyl acetate.* B. p. 116°/764 mm.; M 116·16; n_C 1·38823, n_D 1·39018, n_F 1·39494, $n_{G'}$ 1·39826; R_C 31·48, R_D 31·62, R_F 31·96, $R_{G'}$ 32·20; $Mn_D^{20°}$ 161·49. Densities determined: $d_{4°}^{20°}$ 0·8710, $d_{4°}^{41·5°}$ 0·8449, $d_{4°}^{60·4°}$ 0·8300, $d_{4°}^{85·5°}$ 0·8015. Apparatus *D*.

t.	*H.*	$d_{4°}^{t°}$.	*γ.*	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	*γ.*	*P.*
16·9°	11·09	0·8742	23·94	293·9	61·5°	9·41	0·8289	19·26	293·6
19·4	10·99	0·8716	23·66	293·9	86·9	8·54	0·8009	16·89	294·4
41·0	10·16	0·8504	21·34	293·6				Mean	293·9

194. sec.-*Butyl acetate.* B. p. 112°/765 mm.; M 116·16; n_C 1·38746, n_D 1·38941, n_F 1·39419, $n_{G'}$ 1·39742; R_C 31·40, R_D 31·53, R_F 31·88, $R_{G'}$ 32·11; $Mn_D^{20°}$ 161·39. Densities determined: $d_{4°}^{20°}$ 0·8720, $d_{4°}^{41·5°}$ 0·8482, $d_{4°}^{59·4°}$ 0·8286, $d_{4°}^{86·5°}$ 0·7991. Apparatus *A*.

12·9°	14·86	0·8791	24·46	293·9	41·9°	13·38	0·8478	21·24	294·1
17·2	14·64	0·8748	23·98	293·8	61·9	12·35	0·8264	19·11	293·9
22·1	14·32	0·8699	23·33	293·5	87·4	11·08	0·7982	16·56	293·9
								Mean	293·9

195. tert.-*Butyl acetate.* B. p. 97·5°/763 mm.; M 116·16; n_C 1·38430, n_D 1·38623, n_F 1·39094, $n_{G'}$ 1·39433; R_C 31·36, R_D 31·50, R_F 31·84, $R_{G'}$ 32·20; $Mn_D^{20°}$ 161·02. Densities determined: $d_{4°}^{20°}$ 0·8665, $d_{4°}^{42·2°}$ 0·8444, $d_{4°}^{60·8°}$ 0·8242. Apparatus *A*.

20·4°	13·84	0·8661	22·45	291·9	41·2°	12·74	0·8453	20·17	291·3
25·3	13·57	0·8612	21·89	291·7	61·1	11·63	0·8236	17·95	290·7
								Mean	291·5

196. n-*Amyl acetate.* B. p. 148°/762 mm.; M 130·18; n_C 1·40024, n_D 1·40228, n_F 1·40720, $n_{G'}$ 1·41067; R_C 36·10, R_D 36·27, R_F 36·66, $R_{G'}$ 36·94; $Mn_D^{20°}$ 182·55. Densities determined: $d_{4°}^{20°}$ 0·8745, $d_{4°}^{41·7°}$ 0·8560, $d_{4°}^{61·9°}$ 0·8379, $d_{4°}^{86·7°}$ 0·8128. Apparatus *A*.

20·0°	15·68	0·8745	25·68	335·1	61·4°	13·76	0·8383	21·60	334·9
25·9	15·44	0·8693	25·13	335·3	87·9	12·44	0·8117	18·91	334·4
42·0	14·60	0·8557	23·39	334·6				Mean	334·9

197. iso*Amyl acetate* (from Bisol fermentation alcohol). B. p. 141·5°/761 mm.; M 130·18; n_C 1·39742, n_C 1·40047, n_D 1·40535, $n_{G'}$ 1·40888; R_C 35·99, R_D 36·24, R_F 36·62, $R_{G'}$ 36·91; $Mn_D^{20°}$ 182·32. Densities determined: $d_{4°}^{20°}$ 0·8719, $d_{4°}^{40·0°}$ 0·8541, $d_{4°}^{60·8°}$ 0·8345, $d_{4°}^{85·5°}$ 0·8096. Apparatus *A*.

19·0°	15·27	0·8728	24·96	333·4	60·8°	13·23	0·8342	20·67	332·7
21·1	15·10	0·8709	24·62	333·0	87·9	11·98	0·8072	18·11	332·7
40·1	14·19	0·8542	22·75	332·8				Mean	332·9

198. n-*Hexyl acetate.* B. p. 168·5—169°/765 mm.; M 144·21; n_C 1·40713, n_D 1·40919, n_F 1·41420, $n_{G'}$ 1·41770; R_C 40·73, R_D 40·91, R_F 41·35, $R_{G'}$ 41·66; $Mn_D^{20°}$ 203·22. Densities determined: $d_{4°}^{20°}$ 0·8718, $d_{4°}^{40·8°}$ 0·8544, $d_{4°}^{59·7°}$ 0·8364, $d_{4°}^{85·6°}$ 0·8131. Apparatus *D*.

20·2°	12·31	0·8716	26·50	375·4	59·8°	10·91	0·8363	22·53	375·7
41·3	11·61	0·8540	24·49	375·6	87·2	9·98	0·8117	20·01	375·7
								Mean	375·6

199. *Methyl propionate.* B. p. 79°/762 mm.; M 88·10; n_C 1·37306, n_D 1·37683, n_F 1·38130, $n_{G'}$ 1·38437; R_C 22·04, R_D 22·14, R_F 22·37, $R_{G'}$ 22·53; $Mn_D^{20°}$ 121·30. Densities determined: $d_{4°}^{20°}$ 0·9150, $d_{4°}^{40·3°}$ 0·8914, $d_{4°}^{57·2°}$ 0·8709. Apparatus *A*.

19·5°	14·63	0·9156	25·08	215·3	41·4°	13·39	0·8901	22·32	215·3
26·9	14·31	0·9069	24·30	215·7	56·9	12·51	0·8712	20·41	215·4
								Mean	215·4

200. *Ethyl propionate.* B. p. 98·5°/763 mm.; M 102·13; n_C 1·38200, n_D 1·38394, n_F 1·38847, $n_{G'}$ 1·39180; R_C 26·65, R_D 26·77, R_F 27·06, $R_{G'}$ 27·26; $Mn_D^{20°}$ 141·34. Densities determined: $d_{4°}^{20°}$ 0·8917, $d_{4°}^{42·5°}$ 0·8655, $d_{4°}^{59·6°}$ 0·8457. Apparatus *D*.

16·0°	11·23	0·8963	24·86	254·4	41·0°	10·23	0·8672	21·91	255·0
18·0	11·12	0·8940	24·55	254·3	60·1	9·44	0·8451	19·70	254·9
24·9	10·92	0·8860	23·89	254·8				Mean	254·7

201. n-*Propyl propionate.* B. p. 122°/767 mm.; M 116·16; n_C 1·39125, n_D 1·39319, n_F 1·39792, $n_{G'}$ 1·40131; R_C 31·30, R_D 31·44, R_F 31·76, $R_{G'}$ 32·01; $Mn_D^{20°}$ 161·83. Densities determined: $d_{4°}^{20°}$ 0·8822, $d_{4°}^{41·5°}$ 0·8602, $d_{4°}^{58·8°}$ 0·8353, $d_{4°}^{87·0°}$ 0·8177. Apparatus *A*.

25·8°	14·72	0·8762	24·15	293·9	61·0°	12·97	0·8398	20·40	293·9
40·7	13·97	0·8610	22·52	293·9	86·5	11·64	0·8122	17·70	293·8
								Mean	293·9

202. n-*Butyl propionate.* B. p. 145·5°/767 mm.; M 130·18; n_C 1·39903, n_D 1·40101, n_F 1·40583, $n_{G'}$ 1·40939; R_C 35·99, R_D 36·15, R_F 36·53, $R_{G'}$ 36·81; $Mn_D^{20°}$ 182·38. Densities determined: $d_4^{20°}$ 0·8750, $d_4^{41·5°}$ 0·8556, $d_4^{61·0°}$ 0·8370, $d_4^{88·4°}$ 0·8132. Apparatus *A*.

t.	*H.*	$d_4^{t°}$.	*γ.*	*P.*	*t.*	*H.*	$d_4^{t°}$.	*γ.*	*P.*
15·0°	15·75	0·8797	25·94	334·0	61·5°	13·57	0·8365	21·25	334·2
17·9	15·58	0·8770	25·59	333·8	85·6	12·42	0·8130	18·91	333·9
41·5	14·44	0·8556	23·14	333·7				Mean	333·9

203. *Methyl* n-*butyrate.* B. p. 103°/774 mm.; M 102·13; n_C 1·38357, n_D 1·38729, n_F 1·39193, $n_{G'}$ 1·39528; R_C 26·67, R_D 26·79, 27·07, $R_{G'}$ 27·28; $Mn_D^{20°}$ 141·69. Densities determined: $d_4^{20°}$ 0·8981, $d_4^{40·7°}$ 0·8771, $d_4^{60·4°}$ 0·8537, $d_4^{87·1°}$ 0·8261. Apparatus *A*.

17·5°	15·12	0·9018	25·53	254·6	60·9°	12·83	0·8532	20·50	254·9
27·3	14·54	0·8904	24·24	254·5	87·3	11·30	0·8259	17·48	253·4
40·7	13·93	0·8771	22·88	254·7				Mean	254·4

204. *Ethyl* n-*butyrate.* B. p. 121°/774 mm.; M 116·16; n_C 1·39026, n_D 1·39222, n_F 1·39695, $n_{G'}$ 1·40030; R_C 31·35, R_D 31·48, R_F 31·82, $R_{G'}$ 32·06; $Mn_D^{20°}$ 161·72. Densities determined: $d_4^{20°}$ 0·8790, $d_4^{40·9°}$ 0·8594, $d_4^{60·7°}$ 0·8394, $d_4^{86·5°}$ 0·8113. Apparatus *A*.

19·9°	14·86	0·8791	24·46	293·9	59·8°	12·87	0·8403	20·25	293·3
40·9	13·87	0·8594	22·32	293·8	86·8	11·52	0·8110	17·49	294·2
								Mean	293·8

205. n-*Propyl* n-*butyrate.* B. p. 142·5°/772 mm.; M 130·18; n_C 1·39748, n_D 1·39950, n_F 1·40431, $n_{G'}$ 1·40768; R_C 35·98, R_D 36·14, R_F 36·53, $R_{G'}$ 36·80; $Mn_D^{20°}$ 182·19. Densities determined: $d_4^{20°}$ 0·8722, $d_4^{40·7°}$ 0·8526, $d_4^{61·1°}$ 0·8321, $d_4^{86·6°}$ 0·8073. Apparatus *D*.

15·9°	11·78	0·8762	25·49	333·8	61·2°	10·19	0·8320	20·94	334·7
24·0	11·52	0·8683	24·70	334·2	86·9	9·22	0·8070	18·38	334·0
40·8	10·88	0·8525	22·91	334·1				Mean	334·2

206. n-*Butyl* n-*butyrate.* B. p. 165·5°/773 mm.; M 144·21; n_C 1·40430, n_D 1·40637, n_F 1·41131, $n_{G'}$ 1·41487; R_C 40·61, R_D 40·79, R_F 41·22, $R_{G'}$ 41·54; $Mn_D^{20°}$ 202·81. Densities determined: $d_4^{20°}$ 0·8692, $d_4^{40·4°}$ 0·8516, $d_4^{60·8°}$ 0·8330, $d_4^{85·6°}$ 0·8095. Apparatus *A*.

16·6°	15·99	0·8722	26·11	373·8	60·5°	13·91	0·8333	21·70	373·5
24·5	15·65	0·8652	25·35	374·0	85·9	12·79	0·8091	19·38	374·0
41·6	14·83	0·8505	23·62	373·8				Mean	373·8

207. n-*Amyl* n-*butyrate.* B. p. 185°/757 mm.; M 158·23; n_C 1·41020, n_D 1·41226, n_F 1·41730, $n_{G'}$ 1·42092; R_C 45·30, R_D 45·50, R_F 45·98, $R_{G'}$ 46·33; $Mn_D^{20°}$ 223·47. Densities determined: $d_4^{20°}$ 0·8659, $d_4^{41·4°}$ 0·8475, $d_4^{61·6°}$ 0·8298, $d_4^{86·9°}$ 0·8073. Apparatus *D*.

16·2°	12·37	0·8702	26·58	412·9	62·9°	10·82	0·8287	22·14	414·2
25·2	12·01	0·8614	25·55	413·0	87·5	10·04	0·8068	20·00	414·8
41·7	11·55	0·8472	24·17	414·1				Mean	413·8

208. iso*Amyl* n-*butyrate* (from Bisol fermentation alcohol). B. p. 179·5°/780 mm.; M 158·23; n_C 1·40897, n_D 1·41102, n_F 1·41606, $n_{G'}$ 1·41960; R_C 45·27, R_D 45·46, R_F 45·96, $R_{G'}$ 46·30; $Mn_D^{20°}$ 223·26. Densities determined: $d_4^{20°}$ 0·8642, $d_4^{42·0°}$ 0·8456, $d_4^{60·8°}$ 0·8293, $d_4^{86·5°}$ 0·8058. Apparatus *D*.

16·6°	12·05	0·8671	25·80	411·3	62·1°	10·60	0·8282	21·68	412·2
19·2	11·97	0·8649	25·57	411·4	87·9	9·68	0·8046	19·23	411·8
42·3	11·20	0·8453	23·38	411·6				Mean	411·7

209. *Methyl* iso*butyrate.* B. p. 91·5°/761 mm.; M 102·13; n_C 1·38110, n_D 1·38299, n_F 1·38758, $n_{G'}$ 1·39088; R_C 26·70, R_D 26·82, R_F 27·10, $R_{G'}$ 27·31; $Mn_D^{20°}$ 141·25. Densities determined: $d_4^{20°}$ 0·8884, $d_4^{40·4°}$ 0·8671, $d_4^{60·4°}$ 0·8445. Apparatus *A*.

21·0°	14·20	0·8873	23·59	253·7	40·9°	13·17	0·8665	21·37	253·6
23·7	14·07	0·8844	23·30	253·7	57·9	12·25	0·8472	19·43	253·5
28·5	13·85	0·8793	22·80	253·8				Mean	253·7

210. *Ethyl* iso*butyrate.* B. p. 110°/762 mm.; M 116·16; n_C 138506, n_D 1·38690, n_F 1·39157, $n_{G'}$ 1·39488; R_C 31·35, R_D 31·48, R_F 31·82, $R_{G'}$ 32·06; $Mn_D^{20°}$ 161·10. Densities determined: $d_4^{20°}$ 0·8685, $d_4^{40·4°}$ 0·8479, $d_4^{62·9°}$ 0·8242, $d_4^{86·7°}$ 0·7984. Apparatus *A*.

19·3°	14·26	0·8692	23·21	293·3	41·2°	13·15	0·8471	20·86	293·1
20·2	14·19	0·8683	23·07	293·2	61·4	12·11	0·8258	18·73	292·9
26·0	13·82	0·8623	22·31	292·8	86·3	10·89	0·7988	16·29	292·8
								Mean	293·0

211. n-*Propyl* isobutyrate. B. p. 134°/752 mm.; M 130·18; n_C 1·39356, n_D 1·39552, n_F 1·40033, $n_{G'}$ 1·40383; R_C 35·99, R_D 36·15, R_F 36·53, $R_{G'}$ 36·82; $Mn_D^{20°}$ 181·67. Densities determined: $d_4^{20°}$ 0·8643, $d_4^{41·3°}$ 0·8432, $d_4^{61·4°}$ 0·8236, $d_4^{87·4°}$ 0·7967. Apparatus *D*.

t.	H.	$d_4^{t°}$.	γ.	P.	t.	H.	$d_4^{t°}$.	γ.	P.
15·3°	11·35	0·8690	24·36	332·8	61·5°	9·58	0·8235	19·48	332·0
19·1	11·19	0·8652	23·91	332·7	86·9	8·69	0·7972	17·11	332·1
41·5	10·34	0·8430	21·53	332·6				Mean	332·4

212. n-*Butyl* isobutyrate. B. p. 156°/762 mm.; M 144·21; n_C 1·40056, n_D 1·40248, n_F 1·40739, $n_{G'}$ 1·41098; R_C 40·62, R_D 40·79, R_F 41·23, $R_{G'}$ 41·55; $Mn_D^{20°}$ 202·25. Densities determined: $d_4^{20°}$ 0·8618, $d_4^{41·6°}$ 0·8416, $d_4^{60·9°}$ 0·8239, $d_4^{87·5°}$ 0·7984. Apparatus *A*.

16·4°	15·34	0·8652	24·86	372·2	61·5°	13·21	0·8233	20·34	372·4
18·9	15·24	0·9628	24·62	372·3	86·9	11·98	0·7991	17·93	371·3
42·3	14·12	0·8409	22·23	372·4				Mean	372·1

213. *Methyl* n-*valerate*. B. p. 126·5°/756 mm.; M 116·16; n_C 1·39493, n_D 1·39690, n_F 1·40167, $n_{G'}$ 1·40505; R_C 31·30, R_D 31·44, R_F 31·78, $R_{G'}$ 32·02; $Mn_D^{20°}$ 162·27. Densities determined: $d_4^{20°}$ 0·8895, $d_4^{40·9°}$ 0·8694, $d_4^{61·2°}$ 0·8492, $d_4^{85·0°}$ 0·8236. Apparatus *D*.

19·3°	11·76	0·8902	25·85	294·2	60·0°	10·27	0·8504	21·57	294·4
26·2	11·51	0·8834	25·11	294·4	86·6	9·27	0·8220	18·82	294·7
40·8	10·98	0·8695	23·58	294·4				Mean	294·4

214. *Ethyl* n-*valerate*. B. p. 144°/762 mm.; M 130·18; n_C 1·39843, n_D 1·40042, n_F 1·40525, $n_{G'}$ 1·40869; R_C 36·00; R_D 36·16, R_F 36·55, $R_{G'}$ 36·82; $Mn_D^{20°}$ 182·30. Densities determined: $d_4^{20°}$ 0·8736, $d_4^{41·6°}$ 0·8539, $d_4^{63·8°}$ 0·8331, $d_4^{86·6°}$ 0·8097.

16·3°	15·53	0·8770	25·50	333·6	60·6°	13·46	0·8361	21·07	333·6
20·4	15·38	0·8732	25·15	333·9	87·0	12·19	0·8093	18·47	333·5
41·5	14·38	0·8542	23·00	333·7				Mean	333·6

215. n-*Propyl* n-*valerate*. B. p. 163·5°/750 mm.; M 144·21; n_C 1·40470, n_D 1·40672, n_F 1·41168, $n_{G'}$ 1·41520; R_C 40·59, R_D 40·77, R_F 41·21, $R_{G'}$ 41·52; $Mn_D^{20°}$ 202·86. Densities determined: $d_4^{20°}$ 0·8702, $d_4^{41·1°}$ 0·8514, $d_4^{60·7°}$ 0·8330, $d_4^{86·1°}$ 0·8092. Apparatus *D*.

18·3°	12·07	0·8707	25·95	373·8	61·3°	10·54	0·8324	21·67	373·8
29·1	11·72	0·8619	24·95	373·9	86·7	9·63	0·8087	19·23	373·4
40·9	11·24	0·8516	23·64	373·4				Mean	373·6

216. n-*Butyl* n-*valerate*. B. p. 184°/753 mm.; M 158·23; n_C 1·40992; n_D 1·41197, n_F 1·41703, $n_{G'}$ 1·42055; R_C 45·15, R_D 45·36, R_F 45·84, $R_{G'}$ 46·18; $Mn_D^{20°}$ 223·42. Densities determined: $d_4^{20°}$ 0·8680, $d_4^{40·8°}$ 0·8500, $d_4^{61·7°}$ 0·8313, $d_4^{85·8°}$ 0·8104. Apparatus *A*.

18·2°	16·19	0·8696	26·36	412·3	61·8°	14·21	0·8312	22·12	412·8
26·3	15·89	0·8624	25·66	413·0	86·0	13·17	0·8098	19·57	413·1
40·9	15·11	0·8495	24·04	412·4				Mean	412·7

217. n-*Amyl* n-*valerate*. B. p. 202°/749 mm. and 103°/23 mm.; M 172·26; n_C 1·41412, n_D 1·41635, n_F 1·42128, $n_{G'}$ 1·42499; R_C 49·85, R_D 50·07, R_F 50·60, $R_{G'}$ 50·99; $Mn_D^{20°}$ 243·97. Densities determined: $d_4^{20°}$ 0·8638, $d_4^{40·5°}$ 0·8460, $d_4^{60·1°}$ 0·8298, $d_4^{86·5°}$ 0·8070. Apparatus *E*.

17·1°	13·15	0·8663	26·53	451·3	60·5°	11·66	0·8295	22·53	452·4
40·9	12·31	0·8457	24·24	452·0	88·1	10·73	0·8056	20·13	452·7
								Mean	452·1

218. *Methyl* isovalerate. B. p. 115·5°/760 mm.; M 116·16; n_C 1·39074, n_D 1·39270, n_F 1·39750, $n_{G'}$ 1·40086; R_C 31·31, R_D 31·46, R_F 31·80, $R_{G'}$ 32·04; $Mn_D^{20°}$ 161·78. Densities determined: $d_4^{20°}$ 0·8807, $d_4^{41·5°}$ 0·8592, $d_4^{62·1°}$ 0·8401, $d_4^{86·1°}$ 0·8132. Apparatus *D*.

16·1°	11·29	0·8846	24·66	292·6	42·0°	10·34	0·8587	21·93	292·7
19·9	11·14	0·8808	24·23	292·6	60·7	9·62	0·8395	19·94	292·4
25·3	10·98	0·8753	23·73	292·6	85·9	8·68	0·8134	17·44	292·2
								Mean	292·5

219. *Ethyl* isovalerate. B. p. 134°/771 mm.; M 130·18; n_C 1·39424, n_D 1·39621, n_F 1·40105, $n_{G'}$ 1·40446; R_C 36·01, R_D 36·17, R_F 36·57, $R_{G'}$ 36·84; $Mn_D^{20°}$ 181·76. Densities determined: $d_4^{20°}$ 0·8652, $d_4^{40·9°}$ 0·8456, $d_4^{61·3°}$ 0·8252, $d_4^{85·5°}$ 0·8008. Apparatus *A*.

21·1°	14·72	0·8641	23·82	332·8	61·3°	12·66	0·8252	19·56	331·8
23·0	14·53	0·8623	23·46	332·3	85·0	11·55	0·8013	17·33	331·5
41·4	13·56	0·8451	21·46	331·5				Mean	332·0

220. n-*Propyl* iso*valerate*. B. p. 156°/755 mm.; M 144·21; n_C 1·40116, n_D 1·40312, n_F 1·40814, $n_{G'}$ 1·41168; R_C 40·68, R_D 40·85, R_F 41·29, $R_{G'}$ 41·62; $Mn_D^{20°}$ 202·34. Densities determined: $d_{4°}^{29·6°}$ 0·8617, $d_{4°}^{41·0°}$ 0·8433, $d_{4°}^{61·0°}$ 0·8255, $d_{4°}^{68·4°}$ 0·8025. Apparatus *D*.

t.	*H.*	$d_{4°}$.	γ.	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	γ.	*P.*
18·7°	11·63	0·8629	24·78	372·9	62·1°	10·10	0·8245	20·57	372·5
21·1	11·45	0·8607	24·34	372·1	86·9	9·17	0·8017	18·16	371·3
40·7	10·78	0·8436	22·46	372·1				Mean	372·2

221. n-*Butyl* isovalerate. B. p. 175·5°/755 mm.; M 158·23; n_C 1·40668, n_D 1·40875, n_F 1·41381, $n_{G'}$ 1·41743; R_C 45·22, R_D 45·43, R_F 45·92, $R_{G'}$ 46·27; $Mn_D^{20°}$ 222·91. Densities determined: $d_{4°}^{20°}$ 0·8608, $d_{4°}^{43·6°}$ 0·8401, $d_{4°}^{61·9°}$ 0·8242, $d_{4°}^{86·9°}$ 0·8016. Apparatus *D*.

16·5°	11·96	0·8639	25·52	411·7	61·9°	10·33	0·8242	21·03	411·1
19·3	11·91	0·8614	25·34	412·1	87·3	9·58	0·8012	18·96	410·2
42·4	11·05	0·8411	22·95	411·8				Mean	411·4

222. *Methyl* n-*hexoate*. B. p. 148·5—149·5°/760 mm.; M 130·18; n_C 1·40300, n_D 1·40494, n_F 1·40996, $n_{G'}$ 1·41352; R_C 35·89, R_D 36·05, R_F 36·44, $R_{G'}$ 36·72; $Mn_D^{20°}$ 182·89. Densities determined: $d_{4°}^{20°}$ 0·8850, $d_{4°}^{43·0°}$ 0·8636, $d_{4°}^{61·1°}$ 0·8461, $d_{4°}^{85·1°}$ 0·8230. Apparatus *A*.

14·5°	16·19	0·8902	26·99	333·3	40·9°	14·90	0·8656	24·15	333·4
18·1	15·99	0·8868	26·55	333·2	61·6	13·79	0·8456	21·83	332·8
24·1	15·79	0·8811	26·05	333·8	86·9	12·69	0·8213	19·52	333·2
								Mean	333·3

223. *Ethyl* n-*hexoate*. B. p. 164·5—165°/752 mm.; M 144·21; n_C 1·40512, n_D 1·40712, n_F 1·41217, $n_{G'}$ 1·41563; R_C 40·58, R_D 40·76, R_F 41·20, $R_{G'}$ 41·50; $Mn_D^{20°}$ 202·93. Densities determined: $d_{4°}^{20°}$ 0·8712, $d_{4°}^{41·2°}$ 0·8521, $d_{4°}^{62·6°}$ 0·8330, $d_{4°}^{86·0°}$ 0·8121. Apparatus *A*.

14·5°	16·08	0·8761	26·38	373·0	61·2°	13·97	0·8343	21·82	373·6
18·4	15·89	0·8726	25·96	373·1	85·9	12·85	0·8113	19·52	373·6
41·0	14·89	0·8523	23·76	373·6				Mean	373·4

224. *Methyl* n-*heptoate*. B. p. 171—171·5°/761 mm.; M 144·21; n_C 1·40946, n_D 1·41152, n_F 1·41654, $n_{G'}$ 1·42010; R_C 40·49, R_D 40·66, R_F 41·10, $R_{G'}$ 41·41; $Mn_D^{20°}$ 203·55. Densities determined: $d_{4°}^{20°}$ 0·8815, $d_{4°}^{42·0°}$ 0·8618, $d_{4°}^{61·1°}$ 0·8443, $d_{4°}^{86·0°}$ 0·8225. Apparatus *D*.

16·8°	12·45	0·8844	27·19	372·4	61·8°	10·95	0·8437	22·82	373·6
25·0	12·29	0·8770	26·62	373·5	87·2	10·03	0·8214	20·35	372·9
42·2	11·63	0·8616	24·75	373·3				Mean	373·1

225. *Ethyl* n-*heptoate*. B. p. 185·5—186°/764 mm.; M 158·22; n_C 1·41079, n_D 1·41286, n_F 1·41790, $n_{G'}$ 1·42151; R_C 45·13, R_D 45·33, R_F 45·81, $R_{G'}$ 46·16; $Mn_D^{20°}$ 223·55. Densities determined: $d_{4°}^{20°}$ 0·8702, $d_{4°}^{41·9°}$ 0·8505, $d_{4°}^{62·1°}$ 0·8328, $d_{4°}^{86·5°}$ 0·8117. Apparatus *D*.

20·8°	12·27	0·8695	26·35	412·3	61·9°	10·93	0·8330	22·48	413·6
25·3	12·16	0·8655	25·99	412·8	87·0	10·07	0·8111	20·17	413·4
40·9	11·64	0·8514	24·47	413·3				Mean	413·1

226. *Methyl* n-*octoate*. B. p. 192°/759 mm.; M 158·23; n_C 1·41486, n_D 1·41696, n_F 1·42203, n_G 1·42574; R_C 45·10, R_D 45·30, R_F 45·78, $R_{G'}$ 46·13; $Mn_D^{20°}$ 224·21. Densities determined: $d_{4°}^{20°}$ 0·8784, $d_{4°}^{40·8°}$ 0·8609, $d_{4°}^{60·0°}$ 0·8441, $d_{4°}^{86·8°}$ 0·8208. Apparatus *D*.

11·6°	13·16	0·8856	28·78	413·9	40·6°	12·09	0·8608	25·70	413·9
16·9	12·99	0·8811	28·26	414·1	61·3	11·45	0·8430	23·84	414·7
23·9	12·79	0·8751	27·64	414·6	87·4	10·45	0·8200	21·16	413·9
								Mean	414·2

227. *Ethyl* n-*octoate*. B. p. 205·5—206·5°/742 mm.; M 172·26; n_C 1·41605, n_D 1·41803, n_F 1·42327, $n_{G'}$ 1·42695; R_C 49·74, R_D 49·95, R_F 50·50, $R_{G'}$ 50·88; $Mn_D^{20°}$ 244·28. Densities determined: $d_{4°}^{20°}$ 0·8693, $d_{4°}^{41·5°}$ 0·8505, $d_{4°}^{60·0°}$ 0·8363, $d_{4°}^{86·5°}$ 0·8131. Apparatus *A*.

14·0°	17·06	0·8745	27·94	452·9	60·5°	14·93	0·8350	23·34	453·5
16·3	16·98	0·8725	27·74	453·1	87·1	13·74	0·8126	20·91	453·3
40·9	15·77	0·8511	25·72	455·8				Mean	453·7

228. *Methyl* n-*decoate*. B. p. 228°/758 mm.; M 186·29; n_C 1·42343, n_D 1·42556, n_F 1·43078, $n_{G'}$ 1·43456; R_C 54·37, R_D 54·61, R_F 55·19, $R_{G'}$ 55·62; $Mn_D^{20°}$ 265·57. Densities determined: $d_{4°}^{20°}$ 0·8733, $d_{4°}^{41·5°}$ 0·8559, $d_{4°}^{61·5°}$ 0·8402, $d_{4°}^{86·5°}$ 0·8194. Apparatus *D*.

22·0°	13·16	0·8717	28·33	493·1	62·3°	11·91	0·8396	24·70	494·6
41·4	12·54	0·8560	26·51	493·8	88·1	11·02	0·8184	22·27	494·5
								Mean	494·0

229. *Ethyl* n-*decoate.* B. p. 241·5°/760 mm.; M 200·31; n_C 1·42342, n_D 1·42556, n_F 1·43079, $n_{G'}$ 1·43461; R_C 59·03, R_D 59·30, R_F 59·93, $R_{G'}$ 60·39; $Mn_D^{20°}$ 285·56. Densities determined: $d_4^{20°}$ 0·8648, $d_4^{41·6°}$ 0·8484, $d_4^{61·6°}$ 0·8331, $d_4^{86·6°}$ 0·8131. Apparatus *D*.

t.	*H.*	$d_4^{t°}$.	γ.	*P.*	*t.*	*H.*	$d_4^{t°}$.	γ.	*P.*
16·1°	13·31	0·8678	28·52	533·4	61·9°	11·77	0·8324	24·20	533·7
25·0	13·05	0·8608	27·74	534·1	86·6	11·00	0·8126	22·07	534·3
42·0	12·46	0·8476	26·08	534·1				Mean	533·9

230. n-*Propyl* n-*decoate.* B. p. 115°/4·5 mm.; M 214·34; n_C 1·42581, n_D 1·42797, n_F 1·43324, $n_{G'}$ 1·43697; R_C 63·67, R_D 63·95, R_F 64·63, $R_{G'}$ 65·13; $Mn_4^{20°}$ 306·08. Densities determined: $d_4^{20°}$ 0·8623, $d_4^{41·5°}$ 0·8460, $d_4^{60·5°}$ 0·8310, $d_4^{87·0°}$ 0·8105. Apparatus *D*.

16·5°	13·43	0·8650	28·69	573·5	61·4°	11·94	0·8305	24·49	574·1
20·1	13·28	0·8622	28·28	573·3	88·8	11·17	0·8114	22·38	574·6
40·7	12·63	0·8466	26·41	573·9				Mean	573·9

231. n-*Butyl* n-*decoate.* B. p. 123°/4 mm.; M 228·36; n_C 1·42831, n_D 1·43048, n_F 1·43576, $n_{G'}$ 1·43963; R_C 68·24, R_D 68·55, R_F 69·29, $R_{G'}$ 69·81; $Mn_4^{20°}$ 326·67. Densities determined: $d_4^{20°}$ 0·8614, $d_4^{41·5°}$ 0·8454, $d_4^{61·6°}$ 0·8307, $d_4^{86·6°}$ 0·8112. Apparatus *D*.

19·0	13·43	0·8621	28·59	612·5	61·5°	12·12	0·8306	24·86	613·9
25·2	13·30	0·8575	28·16	613·5	87·2	11·31	0·8108	22·65	614·4
41·7	12·74	0·8453	26·60	613·5				Mean	613·7

232. *Methyl* n-*dodecoate.* B. p. 261·5—262°/766 mm.; M 214·34; n_C 1·42971, n_D 1·43188, n_F 1·43720, $n_{G'}$ 1·44114; R_C 63·60, R_D 63·87, R_F 64·55, $R_{G'}$ 65·06; $Mn_4^{20°}$ 306·91. Densities determined: $d_4^{20°}$ 0·8702, $d_4^{41·6°}$ 0·8533, $d_4^{62·7°}$ 0·8377, $d_4^{86·7°}$ 0·8191. Apparatus D.

13·4°	13·98	0·8753	30·22	574·1	41·8°	13·14	0·8531	27·68	576·3
18·2	13·80	0·8716	29·70	574·1	62·3	12·45	0·8380	25·77	576·3
22·3	13·69	0·8684	29·36	574·5	86·9	11·69	0·8189	23·64	577·1
								Mean	575·4

233. *Ethyl* n-*dodecoate.* B. p. 272·5—273·5°/764 mm.; M 228·36; n_C 1·42890, n_D 1·43108, n_F 1·43639, $n_{G'}$ 1·44025; R_C 68·31, R_D 68·61, R_F 69·35, $R_{G'}$ 69·88; $Mn_4^{20°}$ 326·80. Densities determined: $d_4^{20°}$ 0·8618, $d_4^{39·8°}$ 0·8477, $d_4^{60·1°}$ 0·8324, $d_4^{86·0°}$ 0·8130. Apparatus *A*.

17·1°	17·70	0·8638	28·63	611·5	62·7°	15·82	0·8305	24·60	612·4
41·9	16·64	0·8462	26·37	611·5	88·2	14·80	0·8114	22·49	612·9
								Mean	612·1

234. n-*Propyl* n-*dodecoate.* B. p. 140°/4 mm.; M 242·39; n_C 1·43129, n_D 1·43350, n_F 1·43882, $n_{G'}$ 1·44265; R_C 72·86, R_D 73·18, R_F 73·96, $R_{G'}$ 74·53; $Mn_D^{20°}$ 347·47. Densities determined: $d_4^{20°}$ 0·8617, $d_4^{40·9°}$ 0·8457, $d_4^{61·7°}$ 0·8309, $d_4^{85·7°}$ 0·8124. Apparatus *A*.

13·0°	18·16	0·8670	29·48	651·5	41·4°	17·15	0·8453	27·15	654·5
19·3	17·82	0·8622	28·77	651·1	62·7	16·26	0·8302	25·28	654·7
25·0	17·61	0·8577	28·28	651·7	87·0	15·23	0·8114	23·12	655·1
								Mean	653·1

235. n-*Butyl* n-*dodecoate.* B. p. 153·5°/4·5 mm.; M 256·42; n_C 1·43402, n_D 1·43620, n_F 1·44156, $n_{G'}$ 1·44550; R_C 77·62, R_D 77·97, R_F 78·80, $R_{G'}$ 79·41; $Mn_D^{20°}$ 368·27. Densities determined: $d_4^{20°}$ 0·8603, $d_4^{40·0°}$ 0·8646, $d_4^{60·0°}$ 0·8316, $d_4^{86·1°}$ 0·8127. Apparatus *D*.

13·4°	13·96	0·8651	29·82	692·7	40·8°	13·05	0·8458	27·26	692·7
18·5	13·78	0·8613	29·31	692·7	61·1	12·36	0·8308	25·36	692·6
22·6	13·64	0·8584	28·92	692·7	87·1	11·68	0·8120	23·42	694·7
								Mean	693·0

236. *Diethyl oxalate.* B. p. 183·5°/764 mm.; M 146·14; n_C 1·40807, n_D 1·41023, n_F 1·41542, $n_{G'}$ 1·41918; R_C 33·41, R_D 33·56, R_F 33·93, $R_{G'}$ 34·21; $Mn_D^{20°}$ 206·10. Densities determined: $d_4^{20°}$ 1·0794, $d_4^{41·5°}$ 1·0551, $d_4^{60·8°}$ 1·0335, $d_4^{86·7°}$ 1·0031. Apparatus *D*.

12·2°	12·28	1·0883	33·00	321·8	42·6°	11·33	1·0536	29·48	323·2
17·5	12·10	1·0823	32·34	322·0	61·1	10·75	1·0328	27·42	323·8
23·0	11·96	1·0760	31·78	322·5	87·4	9·94	1·0023	24·60	324·7
								Mean	323·0

237. *Di*-n-*propyl oxalate.* B. p. 211°/749 mm.; M 174·19; n_C 1·4128, n_D 1·41646, n_F 1·42178, $n_{G'}$ 1·42564; R_C 42·76, R_D 42·96, R_F 43·44, $R_{G'}$ 43·78; $Mn_D^{20°}$ 246·74. Densities determined: $d_4^{20°}$ 1·0186, $d_4^{41·6°}$ 0·9979, $d_4^{62·6°}$ 0·9771, $d_4^{86·6°}$ 0·9519. Apparatus *A*.

17·0°	15·89	1·0207	30·37	400·6	41·3°	15·02	0·9976	28·06	401·9
21·9	15·74	1·0167	29·97	400·9	62·0	14·20	0·9771	25·98	402·5
26·5	15·69	1·0121	29·73	401·9	86·1	13·28	0·9518	23·67	403·7
								Mean	401·9

238. *Diisopropyl oxalate.* B. p. 191°/765 mm.; M 174·19; n_C 1·41061, n_D 1·41281, n_F 1·41820, $n_{G'}$ 1·42212; R_C 43·44, R_D 43·65, R_F 44·15, $R_{G'}$ 44·51; $Mn_D^{20°}$ 246·11. Densities determined: $d_{4°}^{20°}$ 0·9947, $d_{4°}^{41·3°}$ 0·9732, $d_{4°}^{62·9°}$ 0·9496, $d_{4°}^{86·4°}$ 0·9244. Apparatus *D*.

t.	*H.*	$d_{4°}^{t°}$.	γ.	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	γ.	*P.*
21·0°	11·55	0·9937	28·34	404·5	62·1°	10·24	0·9504	24·03	405·8
25·1	11·40	0·9894	28·11	405·4	88·3	9·50	0·9224	21·64	407·3
41·2	10·86	0·9733	26·10	404·5				Mean	405·5

239. *Di*-n-*butyl oxalate.* B. p. 242°/773 mm.; M 202·24; n_C 1·42119, n_D 1·42341, n_F 1·42876, $n_{G'}$ 1·43260; R_C 51·96, R_D 52·20, R_F 52·78, $R_{G'}$ 53·19; $Mn_D^{20°}$ 287·87. Densities determined: $d_{4°}^{20°}$ 0·9874, $d_{4°}^{41·5°}$ 0·9684, $d_{4°}^{60·6°}$ 0·9503, $d_{4°}^{86·2°}$ 0·9262. Apparatus *A*.

22·2°	15·94	0·9854	29·41	476·9	63·3°	14·46	0·9479	25·67	480·2
28·2	15·76	0·9800	28·92	478·6	87·3	13·57	0·9252	23·51	481·3
41·3	15·26	0·9686	27·68	478·9				Mean	479·2

240. *Di*-n-*amyl oxalate.* B. p. 139°/9 mm.; M 230·30; n_C 1·42665, n_D 1·42887, n_F 1·43426, $n_{G'}$ 1·43823; R_C 61·16, R_D 61·44, R_F 62·11, $R_{G'}$ 62·59; $Mn_D^{20°}$ 329·08. Densities determined: $d_{4°}^{20°}$ 0·9662, $d_{4°}^{41·4°}$ 0·9483, $d_{4°}^{62·5°}$ 0·9304, $d_{4°}^{86·5°}$ 0·9093. Apparatus *D*.

24·6°	12·30	0·9623	29·23	556·5	62·0°	11·26	0·9308	25·88	558·1
42·0	11·88	0·9478	27·81	558·0	88·1	10·56	0·9079	23·68	559·6
								Mean	558·0

241. *Diisoamyl oxalate* (from Bisol fermentation alcohol). B. p. 127·5°/7 mm.; M 230·30; n_C 1·42488, n_D 1·42712, n_F 1·43253, $n_{G'}$ 1·43643; R_C 61·27, R_D 61·55, R_F 62·23, $R_{G'}$ 62·71; $Mn_D^{20°}$ 328·66. Densities determined: $d_{4°}^{20°}$ 0·9609, $d_{4°}^{41·3°}$ 0·9437, $d_{4°}^{61·2°}$ 0·9266, $d_{4°}^{86·3°}$ 0·9043. Apparatus *D*.

24·8°	11·72	0·9568	27·69	552·4	61·9°	10·79	0·9260	24·68	554·3
41·5	11·32	0·9435	26·38	553·2	87·0	10·17	0·9037	22·70	556·2
								Mean	554·0

242. *Dimethyl succinate.* B. p. 195°/759 mm.; M 146·14; n_C 1·41742, n_D 1·41951, n_F 1·42456, $n_{G'}$ 1·42830; R_C 32·84, R_D 32·99, R_F 33·34, $R_{G'}$ 33·59; $Mn_D^{20°}$ 207·45. Densities determined: $d_{4°}^{20°}$ 1·1198, $d_{4°}^{59·7°}$ 1·0791, $d_{4°}^{85·5°}$ 1·0508, $d_{4°}^{120·1°}$ 1·0132. Apparatus *A*.

17·0°	17·65	1·1229	37·11	321·3	84·9°	14·65	1·0510	28·83	322·2
24·1	17·32	1·1155	36·18	321·3	120·6	13·08	1·0127	24·80	322·0
61·7	15·57	1·0759	31·37	321·5				Mean	321·7

243. *Diethyl succinate.* B. p. 81°/3 mm.; M 174·19; n_C 1·41772, n_D 1·41981, n_F 1·42488, $n_{G'}$ 1·42860; R_C 42·12, R_D 42·30, R_F 42·75, $R_{G'}$ 43·08; $Mn_D^{20°}$ 247·32. Densities determined: $d_{4°}^{20°}$ 1·0416, $d_{4°}^{41·4°}$ 1·0198, $d_{4°}^{60·8°}$ 1·0013, $d_{4°}^{85·2°}$ 0·9759. Apparatus *A*.

20·5°	16·38	1·0411	31·93	397·7	61·2°	14·65	1·0009	27·46	398·4
28·3	16·02	1·0333	31·00	397·8	86·0	13·75	0·9751	25·11	399·9
42·1	15·49	1·0191	29·56	398·5				Mean	398·5

244. *Di*-n-*propyl succinate.* B. p. 101·5°/3 mm.; M 202·24; n_C 1·42296, n_D 1·42521, n_F 1·43038, $n_{G'}$ 1·43425; R_C 51·42, R_D 51·65, R_F 52·20, $R_{G'}$ 52·62; $Mn_D^{20°}$ 288·24. Densities determined: $d_{4°}^{20°}$ 1·0015, $d_{4°}^{41·8°}$ 0·9831, $d_{4°}^{61·4°}$ 0·9647, $d_{4°}^{86·7°}$ 0·9435. Apparatus *D*.

19·6°	12·55	1·0019	31·05	476·5	61·3°	11·24	0·9648	26·78	476·9
26·4	12·13	0·9959	29·76	474·6	87·7	10·51	0·9426	24·47	477·2
41·4	11·81	0·9835	28·68	475·9				Mean	476·2

245. *Diisopropyl succinate.* B. p. 82°/3 mm.; M 202·24; n_C 1·41562, n_D 1·41771, n_F 1·42284, $n_{G'}$ 1·42650; R_C 51·49, R_D 51·72, R_F 52·28, $R_{G'}$ 52·68; $Mn_D^{20°}$ 286·72. Densities determined: $d_{4°}^{20°}$ 0·9847, $d_{4°}^{41·1°}$ 0·9653, $d_{4°}^{60·5°}$ 0·9467, $d_{4°}^{86·0°}$ 0·9221. Apparatus *D*.

18·5°	11·62	0·9861	28·30	473·0	61·3°	10·42	0·9460	24·34	474·9
25·8	11·50	0·9792	27·81	474·3	85·1	9·75	0·9230	22·22	475·7
41·3	11·02	0·9651	26·27	474·4				Mean	474·3

246. *Di*-n-*butyl succinate.* B. p. 121°/3 mm.; M 230·30; n_C 1·42777, n_D 1·42992, n_F 1·43519, $n_{G'}$ 1·43904; R_C 60·63, R_D 60·89, R_F 61·55, $R_{G'}$ 62·01; $Mn_D^{20°}$ 329·30. Densities determined: $d_{4°}^{20°}$ 0·9768, $d_{4°}^{41·0°}$ 0·9602, $d_{4°}^{62·0°}$ 0·9427, $d_{4°}^{86·5°}$ 0·9213. Apparatus *D*.

16·7°	12·80	0·9795	30·96	554·6	60·7°	11·53	0·9438	26·87	555·6
24·2	12·57	0·9734	30·22	554·7	87·2	10·74	0·9207	24·42	556·0
41·5	12·11	0·9598	28·70	555·4				Mean	555·3

247. *Diisobutyl succinate.* B. p. 116°/4 mm.; M 230·30; n_C 1·42450, n_D 1·42666, n_F 1·43190, $n_{G'}$ 1·43571; R_C 60·81, R_D 61·08, R_F 61·73, $R_{G'}$ 62·20; $Mn_D^{20°}$ 328·57. Densities determined: $d_{4°}^{20°}$ 0·9675, $d_{4°}^{41·5°}$ 0·9498, $d_{4°}^{60·4°}$ 0·9337, $d_{4°}^{86·6°}$ 0·9110. Apparatus *D*.

t.	*H.*	$d_{4°}^{t°}$.	γ.	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	γ.	*P.*
20·3°	11·90	0·9672	28·42	549·8	60·7°	10·79	0·9334	24·87	551·0
28·1	11·71	0·9607	27·85	550·4	86·9	10·15	0·9107	22·83	552·8
41·6	11·32	0·9497	26·55	550·5				Mean	550·9

248. *Di-n-amyl succinate.* B. p. 129°/2 mm.; M 258·35; n_C 1·43208, n_D 1·43425, n_F 1·43959, $n_{G'}$ 1·44349; R_C 69·83, R_D 70·14, R_F 70·88, $R_{G'}$ 71·43; $Mn_D^{20°}$ 370·55. Densities determined: $d_{4°}^{20°}$ 0·9598, $d_{4°}^{41·9°}$ 0·9435, $d_{4°}^{62·3°}$ 0·9272, $d_{4°}^{86·9°}$ 0·9078. Apparatus *D*.

23·6°	12·64	0·9570	29·87	631·1	60·9°	11·81	0·9283	27·07	634·8
42·0	12·28	0·9434	28·61	633·3	87·5	11·06	0·9073	24·78	635·3
								Mean	633·6

249A. *Diisoamyl succinate* (from Sharples synthetic alcohol). B. p. 130°/4 mm.; M 258·35; n_C 1·43132, n_C 1·43355, n_D 1·43886, $n_{G'}$ 1·44275; R_C 69·85, R_D 70·18, R_F 70·92, $R_{G'}$ 71·47; $Mn_D^{20°}$ 370·37. Densities determined: $d_{4°}^{20°}$ 0·9579, $d_{4°}^{41·4°}$ 0·9429, $d_{4°}^{60·4°}$ 0·9278, $d_{4°}^{86·3°}$ 0·9067. Apparatus *D*.

21·5°	12·63	0·9568	29·84	631·1	61·7°	11·54	0·9268	26·41	631·9
24·6	12·49	0·9545	29·44	630·5	87·9	10·77	0·9054	24·08	632·1
41·2	12·08	0·9431	28·14	630·9				Mean	631·3

249B. *Diisoamyl succinate* (from Bisol fermentation alcohol). B. p. 150°/9 mm.; M 258·35; n_C 1·43053, n_D 1·43274, n_F 1·43803, $n_{G'}$ 1·44206; R_C 69·89, R_D 70·21, R_F 70·95, $R_{G'}$ 71·53; $Mn_D^{20°}$ 370·14. Densities determined: $d_{4°}^{20°}$ 0·9579, $d_{4°}^{40·6°}$ 0·9403, $d_{4°}^{61·1°}$ 0·9228, $d_{4°}^{86·6°}$ 0·9032. Apparatus *C*.

18·6°	12·95	0·9569	29·42	628·8	61·1°	11·60	0·9228	25·41	628·6
41·0	12·46	0·9395	27·79	631·4	86·8	11·05	0·9030	23·69	631·2
								Mean	630·0

The measurements of the capillary rise were not altogether satisfactory because of the slow response to rise of temperature which was doubtless connected with the high viscosity of the liquid.

250. *Dimethyl adipate.* B. p. 120·5°/17 mm.; M 174·19; n_C 1·42618, n_D 1·42832, n_F 1·43349, $n_{G'}$ 1·43720; R_C 42·02, R_D 42·20, R_F 42·65, $R_{G'}$ 42·97; $Mn_D^{20°}$ 248·80. Densities determined: $d_{4°}^{20°}$ 1·0625, $d_{4°}^{41·0°}$ 1·0434, $d_{4°}^{60·4°}$ 1·0244, $d_{4°}^{86·8°}$ 1·0002. Apparatus *D*.

18·2°	13·76	1·0642	36·16	401·4	61·2°	12·37	1·0236	31·27	402·4
22·4	13·69	1·0602	35·84	402·0	86·7	11·53	0·9989	28·44	402·7
41·2	12·98	1·0432	33·44	401·5				Mean	402·0

251. *Diethyl adipate.* B. p. 134·5°/17 mm.; M 202·24; n_C 1·42551, n_D 1·42767, n_F 1·43287, $n_{G'}$ 1·43650; R_C 51·31, R_D 51·54, R_F 52·09, $R_{G'}$ 52·47; $Mn_D^{20°}$ 288·74. Densities determined: $d_{4°}^{20°}$ 1·0088, $d_{4°}^{41·7°}$ 0·9881, $d_{4°}^{61·4°}$ 0·9698, $d_{4°}^{86·6°}$ 0·9473. Apparatus *A*.

24·1°	17·04	1·0050	32·07	478·9	62·0°	15·38	0·9692	27·91	479·6
41·1	16·23	0·9887	30·05	478·9	86·7	14·36	0·9463	25·45	480·0
								Mean	479·4

252. *Di-n-propyl adipate.* B. p. 146°/9 mm.; M 230·32; n_C 1·42924, n_D 1·43143, n_F 1·43669, $n_{G'}$ 1·44044; R_C 60·55, R_D 60·82, R_F 61·48, $R_{G'}$ 61·93; $Mn_D^{20°}$ 329·68. Densities determined: $d_{4°}^{20°}$ 0·9810, $d_{4°}^{41·1°}$ 0·9629, $d_{4°}^{61·1°}$ 0·9453, $d_{4°}^{86·6°}$ 0·9243. Apparatus *A*.

9·7°	17·68	0·9899	32·77	556·7	42·3°	16·44	0·9619	29·61	558·6
16·2	17·45	0·9843	32·16	557·2	62·4	15·63	0·9442	27·63	559·3
22·4	17·32	0·9789	31·75	558·5	86·0	14·72	0·9242	25·36	559·2
								Mean	558·2

253. *Diisopropyl adipate.* B. p. 120°/6·5 mm.; M 230·32; n_C 1·42252, n_D 1·42466, n_F 1·42983, $n_{G'}$ 1·43343; R_C 60·65, R_D 60·93, R_F 61·57, $R_{G'}$ 62·02; $Mn_D^{20°}$ 328·14. Densities determined: $d_{4°}^{20°}$ 0·9659, $d_{4°}^{41·3°}$ 0·9455, $d_{4°}^{61·0°}$ 0·9277, $d_{4°}^{86·0°}$ 0·9054. Apparatus *D*.

17·7°	12·41	0·9679	29·66	555·4	61·6°	10·92	0·9271	25·00	555·6
22·0	12·23	0·9640	29·12	555·0	87·1	10·24	0·9044	22·87	556·9
41·2	11·66	0·9456	27·23	556·4				Mean	555·9

254. *Di-n-butyl adipate.* B. p. 158·5°/7 mm.; M 258·35; n_C 1·43304, n_D 1·43525, n_F 1·44055, $n_{G'}$ 1·44434; R_C 69·77, R_D 70·09, R_F 70·84, $R_{G'}$ 71·35; $Mn_D^{20°}$ 370·81. Densities determined: $d_{4°}^{20°}$ 0·9624, $d_{4°}^{41·6°}$ 0·9448, $d_{4°}^{61·5°}$ 0·9282, $d_{4°}^{87·1°}$ 0·9093. Apparatus *D*.

15·9°	13·29	0·9657	31·69	634·8	61·0°	12·04	0·9286	27·61	637·7
22·4	13·16	0·9605	31·22	635·8	87·7	11·29	0·9093	25·35	637·7
41·0	12·65	0·9453	29·53	637·1				Mean	636·6

255. *Di*-n-*amyl adipate.* B. p. 185·5°/10 mm.; *M* 286·40; n_C 1·43644, n_D 1·43867, n_F 1·44406, $n_{G'}$ 1·44792; R_C 79·03, R_D 79·39, R_F 80·23, $R_{G'}$ 80·83; $Mn_D^{20°}$ 412·04. Densities determined: $d_4^{20°}$ 0·9478, $d_4^{41·5°}$ 0·9316, $d_4^{61·1°}$ 0·9159, $d_4^{86·4°}$ 0·8974. Apparatus *D*.

t.	*H.*	$d_4^{t°}$.	γ.	*P.*	*t.*	*H.*	$d_4^{t°}$.	γ.	*P.*
15·3°	13·46	0·9514	31·63	713·9	61·4°	12·20	0·9161	27·60	716·6
41·4	12·80	0·9319	29·46	716·0	85·1	11·54	0·8985	25·61	717·0
								Mean	715·9

256. *Diisoamyl adipate* (from Bisol fermentation alcohol). B. p. 184·5°/13 mm.; *M* 286·40; n_C 1·43498, n_D 1·43721, n_F 1·44258, $n_{G'}$ 1·44646; R_C 79·05, R_D 79·40, R_F 80·25, $R_{G'}$ 80·87; $Mn_D^{20°}$ 411·62. Densities determined: $d_4^{20°}$ 0·9454, $d_4^{41·5°}$ 0·9286, $d_4^{60·7°}$ 0·9130, $d_4^{86·2°}$ 0·8931. Apparatus *D*.

22·1°	12·87	0·9437	29·99	710·2	61·4°	11·83	0·9123	26·65	713·3
42·0	12·27	0·9282	28·13	710·6	87·3	11·08	0·8924	24·43	713·2
								Mean	711·8

257. *Dimethyl suberate.* B. p. 120°/6 mm.; *M* 202·24; n_C 1·43163, n_D 1·43380, n_F 1·43908, $n_{G'}$ 1·44303; R_C 51·19, R_D 51·42, R_F 51·97, $R_{G'}$ 52·37; $Mn_D^{20°}$ 289·97. Densities determined: $d_4^{20°}$ 1·0238, $d_4^{40·9°}$ 1·0048, $d_4^{61·0°}$ 0·9869, $d_4^{86·5°}$ 0·9645. Apparatus *D*.

14·5°	14·23	1·0288	36·15	482·0	61·4°	12·69	0·9865	30·92	483·4
22·0	14·13	1·0220	35·66	483·6	86·1	11·93	0·9649	28·43	484·0
42·1	13·36	1·0037	33·12	483·4				Mean	483·3

258. *Diethyl suberate.* B. p. 131°/5 mm.; *M* 230·30; n_C 1·43003, n_D 1·43219, n_F 1·43748, $n_{G'}$ 1·44465; R_C 60·64, R_D 60·91, R_F 61·56, $R_{G'}$ 62·13; $Mn_{D_1}^{20°}$ 329·83. Densities determined: $d_4^{20°}$ 0·9811, $d_4^{41·5°}$ 0·9634, $d_4^{59·1°}$ 0·9490, $d_4^{85·6°}$ 0·9261. Apparatus *D*.

13·5°	13·63	0·9865	33·21	560·4	41·1°	12·82	0·9637	30·51	561·7
17·8	13·51	0·9829	32·79	560·7	88·7	11·37	0·9235	25·93	562·7
23·3	13·34	0·9784	32·33	560·9				Mean	561·4

259. *Di*-n-*propyl suberate.* B. p. 165°/8 mm.; *M* 258·35; n_C 1·43317, n_D 1·43535, n_F 1·44070, $n_{G'}$ 1·44465; R_C 69·82, R_D 70·13, R_F 70·87, $R_{G'}$ 71·43; $Mn_D^{20°}$ 370·84. Densities determined: $d_4^{20°}$ 0·9621, $d_4^{42·0°}$ 0·9438, $d_4^{61·5°}$ 0·9285, $d_4^{86·0°}$ 0·9086. Apparatus *D*.

16·8°	13·48	0·9647	32·12	637·5	61·9°	12·24	0·9282	28·06	640·6
23·2	13·36	0·9595	31·66	638·7	85·4	11·55	0·9090	25·93	641·3
41·0	12·83	0·9446	29·93	639·7				Mean	639·6

260. *Di*-n-*butyl suberate.* B. p. 175·5°/4·5 mm.; *M* 286·40; n_C 1·43631, n_D 1·43852, n_F 1·44387, $n_{G'}$ 1·44777; R_C 79·02, R_D 79·36, R_F 80·21, $R_{G'}$ 80·82; $Mn_D^{20°}$ 411·99. Densities determined: $d_4^{20°}$ 0·9483, $d_4^{41·5°}$ 0·9319, $d_4^{60·8°}$ 0·9169, $d_4^{85·9°}$ 0·8978. Apparatus *A*.

17·2°	17·96	0·9504	31·96	716·5	40·7°	17·02	0·9328	29·73	716·9
20·5	17·77	0·9479	31·54	716·0	62·1	16·24	0·9179	27·91	717·2
27·9	17·64	0·9423	31·13	717·9	86·3	15·29	0·8975	25·70	718·3
								Mean	717·1

261. *Diethyl sebacate.* B. p. 156°/6 mm.; *M* 258·35; n_C 1·43440, n_D 1·43660, n_F 1·44193, $n_{G'}$ 1·44578; R_C 69·85, R_D 70·16, R_F 70·90, $R_{G'}$ 71·44; $Mn_D^{20°}$ 371·15. Densities determined: $d_4^{20°}$ 0·9640, $d_4^{43·2°}$ 0·9456, $d_4^{61·9°}$ 0·9310, $d_4^{85·8°}$ 0·9114. Apparatus *A*.

20·1°	18·14	0·9639	32·74	641·1	61·9°	16·48	0·9310	28·73	642·5
27·3	17·94	0·9582	32·19	642·3	87·1	15·48	0·9104	26·37	643·1
43·5	17·15	0·9454	30·36	641·5				Mean	642·1

262. *Di*-n-*propyl sebacate.* B. p. 178—179°/5 mm.; *M* 286·40; n_C 1·43695, n_D 1·43913, n_F 1·44453, $n_{G'}$ 1·44841; R_C 79·01, R_D 79·34, R_F 80·19, $R_{G'}$ 80·80; $Mn_D^{20°}$ 412·10. Densities determined: $d_4^{20°}$ 0·9495, $d_4^{40·7°}$ 0·9336, $d_4^{60·6°}$ 0·9179, $d_4^{85·9°}$ 0·8983. Apparatus *A*.

20·4°	18·15	0·9492	32·26	719·0	61·9°	16·54	0·9169	28·40	721·0
27·9	17·99	0·9433	31·78	720·8	86·7	15·58	0·8977	26·19	721·6
41·2	17·39	0·9332	30·39	720·5				Mean	720·6

263. *Dimethyl methylmalonate.* B. p. 176—176·5°/761 mm; *M* 146·14; n_C 1·41070, n_D 1·41276, n_F 1·41770, $n_{G'}$ 1·42141; R_C 33·04, R_D 33·18, R_F 33·53, $R_{G'}$ 33·79; $Mn_D^{20°}$ 206·47. Densities determined: $d_4^{20°}$ 1·0977, $d_4^{40·6°}$ 1·0751, $d_4^{61·2°}$ 1·0528, $d_4^{86·2°}$ 1·0247. Apparatus *A*.

14·9°	16·49	1·1033	34·07	320·0	41·0°	15·36	1·0747	30·90	320·6
20·3	16·35	1·0974	33·60	320·6	61·0	14·44	1·0530	28·47	320·6
24·2	16·15	1·0931	33·06	320·6	85·9	13·37	1·0250	25·66	320·9
								Mean	320·6

264. *Diethyl methylmalonate.* B. p. 195·5—196°/773 mm.; M 174·19; n_C 1·41052, n_D 1·41261, n_F 1·41770, $n_{G'}$ 1·42125; R_C 42·25, R_D 42·44, R_F 42·90, $R_{G'}$ 43·23; $Mn_D^{20°}$ 246·06. Densities determined: $d_4^{20°}$ 1·0225, $d_4^{40·8°}$ 1·0020, $d_4^{60·6°}$ 0·9816, $d_4^{86·8°}$ 0·9552. Apparatus *D*.

t.	*H.*	$d_4^{t°}$.	γ.	*P.*	*t.*	*H.*	$d_4^{t°}$.	γ.	*P.*
16·5°	11·97	1·0260	30·33	398·4	41·4°	11·22	1·0014	27·75	399·2
21·2	11·82	1·0213	29·81	398·5	60·3	10·53	0·9819	25·53	398·2
24·2	11·74	1·0183	29·52	398·7	80·4	9·94	0·9616	23·61	399·3
								Mean	398·7

265. *Di*-n-*propyl methylmalonate.* B. p. 222·5—226°/771 mm.; M 202·24; n_C 141705, n_D 1·41906, n_F 1·42431, $n_{G'}$ 1·42799; R_C 51·57, R_D 51·79, R_F 52·34, $R_{G'}$ 52·74; $Mn_D^{20°}$ 287·02. Densities determined: $d_4^{20°}$ 0·9865, $d_4^{41·6°}$ 0·9675, $d_4^{59·9°}$ 0·9506, $d_4^{85·1°}$ 0·9271. Apparatus *A*.

15·9°	15·93	0·9902	29·54	476·1	41·4°	14·90	0·9677	27·00	476·4
18·5	15·81	0·9880	29·25	476·0	62·0	14·04	0·9487	24·88	476·4
22·9	15·65	0·9839	28·83	476·3	87·4	13·02	0·9249	22·55	476·5
								Mean	476·3

266. *Di*-n-*butyl methylmalonate.* B. p. 254·5—255·5°/761 mm.; M 230·30; n_C 1·42291, n_D 1·42506, n_F 1·43030, $n_{G'}$ 1·43413; R_C 60·89, R_D 61·02, R_F 61·68, $R_{G'}$ 62·15; $Mn_D^{20°}$ 328·20. Densities determined: $d_4^{20°}$ 0·9652, $d_4^{40·8°}$ 0·9472, $d_4^{61·9°}$ 0·9294, $d_4^{87·1°}$ 0·9085. Apparatus *D*.

19·4°	12·08	0·9657	28·81	552·5	60·5°	10·94	0·9297	25·12	554·6
41·2	11·53	0·9476	26·98	553·8	87·2	10·13	0·9067	22·68	554·3
								Mean	553·8

267. *Dimethyl ethylmalonate.* B. p. 85°/15 mm.; M 160·17; n_C 1·41555, n_D 1·41781, n_F 1·42273, $n_{G'}$ 1·42633; R_C 37·63, R_D 37·82, R_F 38·21, $R_{G'}$ 38·49; $Mn_D^{20°}$ 227·09. Densities determined: $d_4^{20°}$ 1·0669, $d_4^{41·6°}$ 1·0442, $d_4^{65·2°}$ 1·0200, $d_4^{85·2°}$ 0·9997. Apparatus E.

18·3°	13·12	1·0686	32·65	358·3	59·2°	11·71	1·0262	27·99	359·0
25·1	12·84	1·0616	31·75	358·1	86·7	10·66	0·9982	24·78	358·0
40·8	12·31	1·0444	29·94	358·7				Mean	358·4

268. *Diethyl ethylmalonate.* B. p. 109°/24 mm.; M 188·23; n_C 1·41437, n_D 1·41656, n_F 1·42151, $n_{G'}$ 1·42525; R_C 46·85, R_D 47·07, R_F 47·56, $R_{G'}$ 47·94; $Mn_D^{20°}$ 266·63. Densities determined: $d_4^{20°}$ 1·0047, $d_4^{40·6°}$ 0·9845, $d_4^{61·1°}$ 0·9651, $d_4^{61·1°}$ 0·9651, $d_4^{85·7°}$ 0·9412. Apparatus *E*.

16·3°	12·76	1·0083	29·96	436·7	63·0°	11·14	0·9633	24·99	436·9
20·8	12·60	1·0039	29·46	436·8	86·7	10·43	0·9402	22·84	437·5
40·3	11·93	0·9848	27·36	437·1				Mean	437·0

269. *Di*-n-*propyl ethylmalonate.* B. p. 123°/15 mm.; M 216·27; n_C 1·42022, n_D 1·42246, n_F 1·42748, $n_{G'}$ 1·43127; R_C 56·17, R_D 56·44, R_F 57·02, $R_{G'}$ 57·47; $Mn_D^{20°}$ 307·64. Densities determined: $d_4^{20°}$ 0·9748, $d_4^{42·6°}$ 0·9552, $d_4^{61·3°}$ 0·9379, $d_4^{85·6°}$ 0·9159. Apparatus E.

15·1°	12·98	0·9792	29·60	514·7	61·6°	11·40	0·9376	24·89	515·0
19·6	12·77	0·9752	29·00	514·5	84·8	10·78	0·9167	23·02	516·5
41·4	12·06	0·9558	26·85	514·9				Mean	515·1

270. *Di*-n-*butyl ethylmalonate.* B. p. 145°/14 mm.; M 244·32; n_C 1·42504, n_D 1·42732, n_F 1·43239, $n_{G'}$ 1·43628; R_C 65·31, R_D 65·62, R_F 66·30, $R_{G'}$ 66·82; $Mn_D^{20°}$ 348·72. Densities determined: $d_4^{20°}$ 0·9566, $d_4^{41·6°}$ 0·9394, $d_4^{60·9°}$ 0·9221, $d_4^{86°}$ 0·9003. Apparatus *E*.

16·4°	13·06	0·9596	29·19	591·8	61·5°	11·58	0·9216	24·86	591·9
18·9	12·94	0·9575	28·86	591·4	87·1	10·86	0·9000	22·76	593·0
40·9	12·30	0·9395	26·91	592·0				Mean	592·0

271. *Dimethyl* n-*propylmalonate.* B. p. 203·5—204°/760 mm.; M 174·19; n_C 1·41905, n_D 1·42121, n_F 1·42632, $n_{G'}$ 1·43012; R_C 42·23, R_D 42·42, R_F 42·87, $R_{G'}$ 43·20; $Mn_D^{20°}$ 247·56. Densities determined: $d_4^{20°}$ 1·0418, $d_4^{41·3°}$ 1·0204, $d_4^{63·3°}$ 0·9996, $d_4^{85·9°}$ 0·9767. Apparatus *D*.

16·9°	12·27	1·0449	31·66	395·4	61·9°	10·88	1·0007	26·89	396·4
25·2	12·06	1·0366	30·87	396·1	87·1	10·12	0·9755	24·38	396·8
41·9	11·49	1·0198	28·94	396·2				Mean	396·2

272. *Diethyl* n-*propylmalonate.* B. p. 221—221·5°/767 mm.; M 202·24; n_C 1·41748, n_D 1·41966, n_F 1·42475, $n_{G'}$ 1·42851; R_C 51·57, R_D 51·81, R_F 52·36, $R_{G'}$ 52·76; $Mn_D^{20°}$ 287·12. Densities determined: $d_4^{20°}$ 0·9873, $d_4^{40·6°}$ 0·9682, $d_4^{62·5°}$ 0·9470, $d_4^{85·6°}$ 0·9259. Apparatus *A*.

19·9°	15·68	0·9874	28·99	475·3	62·2°	13·93	0·9482	24·73	475·6
24·0	15·52	0·9836	28·58	475·4	87·4	12·94	0·9244	22·40	475·9
42·4	14·72	0·9665	26·64	475·4				Mean	475·5

273. *Di*-n-*propyl* n-*propylmalonate*. B. p. 121°/6 mm.; M 230·30, n_C 1·42300, n_D 1·42516, n_F 1·43039, $n_{G'}$ 1·43418; R_C 60·81, R_D 61·08, R_F 61·73, $R_{G'}$ 62·21; $Mn_D^{20°}$ 328·22. Densities determined: $d_{4°}^{20°}$ 0·9644, $d_{4°}^{41·2°}$ 0·9461, $d_{4°}^{60·9°}$ 0·9287, $d_{4°}^{66·4°}$ 0·9068. Apparatus *D*.

t.	H.	$d_{4°}^{t°}$.	γ.	P.	t.	H.	$d_{4°}^{t°}$.	γ.	P.
22·1°	12·02	0·9626	28·57	553·1	61·5°	10·80	0·9282	24·76	553·4
41·7	11·36	0·9457	26·53	552·7	85·9	10·10	0·9064	22·61	554·0
								Mean	553·3

274. *Di*-n-*butyl* n-*propylmalonate*. B. p. 150°/9 mm.; M 258·35; n_C 1·42700, n_D 1·42917, n_F 1·43477, $n_{G'}$ 1·43831; R_C 69·99, R_D 70·30, R_F 71·06, $R_{G'}$ 71·60; $Mn_D^{20°}$ 369·24. Densities determined: $d_{4°}^{20°}$ 0·9477, $d_{4°}^{40·7°}$ 0·9305, $d_{4°}^{59·5°}$ 0·9151, $d_{4°}^{65·1°}$ 0·8939. Apparatus *D*.

19·4°	12·17	0·9482	28·50	629·5	61·3°	11·0 0	0·9136	24·82	631·2
41·1	11·56	0·9302	26·56	630·5	87·1	10·28	0·8922	22·65	631·7
								Mean	630·7

275. *Dimethyl* n-*amylmalonate*. B. p. 104°/4·5 mm.; M 202·26; n_C 1·42548, n_D 1·42767, n_F 1·43292, $n_{G'}$ 1·43669; R_C 51·55, R_D 51·79, R_F 52·34, $R_{G'}$ 52·74; $Mn_D^{20°}$ 288·76. Densities determined: $d_{4°}^{20°}$ 1·0042, $d_{4°}^{41·7°}$ 0·9849, $d_{4°}^{62·6°}$ 0·9665, $d_{4°}^{87·3°}$ 0·9452. Apparatus *D*.

16·3°	12·44	1·0075	30·95	473·5	40·4°	11·72	0·9816	28·54	474·1
21·4	12·26	1·0030	30·37	473·4	61·4	11·09	0·9676	26·50	474·3
22·7	12·21	1·0016	30·20	473·4	86·0	10·39	0·9463	24·28	474·5
								Mean	473·9

276. *Diethyl* n-*amylmalonate*. B. p. 113°/3·5 mm.; M 230·32; n_C 1·42328, n_D 1·42546, n_F 1·43065, $n_{G'}$ 1·43442; R_C 60·80, R_D 61·08, R_F 61·73, $R_{G'}$ 62·19; $Mn_D^{20°}$ 328·32. Densities determined: $d_{4°}^{20°}$ 0·9652, $d_{4°}^{41·0°}$ 0·9473, $d_{4°}^{60·8°}$ 0·9306, $d_{4°}^{86·8°}$ 0·9068. Apparatus *D*.

16·1°	12·29	0·9686	92·40	553·7	61·9°	10·86	0·9297	24·93	553·6
19·6	12·12	0·9655	28·90	553·1	86·8	10·10	0·9068	22·62	553·9
42·1	11·38	0·9464	26·60	552·7				Mean	553·4

277. *Di*-n-*propyl* n-*amylmalonate*. B. p. 136·5°/4 mm.; M 258·35; n_C 1·42729, n_D 1·42947, n_F 1·43475, $n_{G'}$ 1·43865; R_C 70·06, R_D 70·37, R_F 71·12, $R_{G'}$ 71·68; $Mn_D^{20°}$ 369·40. Densities determined: $d_{4°}^{20°}$ 0·9474, $d_{4°}^{41·0°}$ 0·9307, $d_{4°}^{60·4°}$ 0·9151, $d_{4°}^{86·1°}$ 0·8929. Apparatus *D*.

17·0°	12·35	0·9498	28·97	631·0	60·8°	11·10	0·9148	25·08	632·0
40·6	11·67	0·9310	26·83	631·6	86·1	10·35	0·8929	22·77	632·5
								Mean	631·8

278. *Di*-n-*butyl* n-*amylmalonate*. B. p. 152·5°/3·5 mm.; M 286·36; n_C 1·43070, n_D 1·43289, n_F 1·43822, $n_{G'}$ 1·44213; R_C 79·32, R_D 79·67, R_F 80·52, $R_{G'}$ 81·15; $Mn_D^{20°}$ 410·33. Densities determined: $d_{4°}^{20°}$ 0·9339, $d_{4°}^{40·0°}$ 0·9192, $d_{4°}^{60·1°}$ 0·9032, $d_{4°}^{85·7°}$ 0·8828. Apparatus *A*.

21·3°	16·19	0·9329	28·35	707·9	60·8°	14·79	0·9027	25·00	709·3
41·3	15·51	0·9182	26·67	708·7	86·5	13·86	0·8822	22·90	710·0
								Mean	709·0

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131. *Physical Properties and Chemical Constitution. Part XIV. The Parachors and the Refractivities of the Halogens.*

By ARTHUR I. VOGEL.

Determination have been made of the refractivities for the C, D, F, and G′ lines at 20° and of the parachors of a number of miscellaneous halogen compounds, which include polymethylene chlorides, bromides, and iodides, alkyl chloro-, bromo-, and iodo-acetates, alkyl fluorides, and aromatic fluorine compounds. The new experimental data and those for the alkyl chlorides, bromides, and iodides (Part VIII, *J.*, 1943, 636) have been employed for the calculation of the parachors and refractivities of chlorine, bromine, and iodine by three independent methods, *viz.*, (1) from the alkyl halides and hydrocarbons (Part IX, *J.*, 1946, 133) or alkyl groups (Part XI, this vol., p. 610); (2) from the polymethylene dihalides $X{\cdot}[CH_2]_n{\cdot}X$ and CH_2 (Part IX, *loc. cit.*); and (3) from the alkyl monohalogenoacetates $CH_2X{\cdot}CO_2R$ and the dialkyl succinates $[CH_2]_2(CO_2R)_2$. The results by these three methods are in reasonable agreement and the mean values are:

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
Cl	55·2	5·821	5·844	5·918	5·973	50·41
Br	68·8	8·681	8·741	8·892	9·011	118·07
I	90·3	13·825	13·954	14·310	14·620	196·27
F	26·1	0·81	0·81	0·79	0·78	21·84

The constants for fluorine, derived from four alkyl fluorides, must be regarded as preliminary and approximate.

THE methods of derivation and the published values of the parachors and refractivities of the halogen elements cannot be regarded as altogether trustworthy. For instance, the parachor of chlorine has been deduced (Sugden, " The Parachor and Valency ", 1930, p. 37) from the parachors of CCl_4, $CHCl_3$, CH_2Cl_2, $C_2H_2Cl_4$, $CH_2Cl{\cdot}CH_2Cl$, $CH_2{\cdot}CHCl_2$, C_3H_7Cl, and $C_5H_{11}Cl$: the extreme values were 52·0 and 57·7, and the " weighted mean " 54·3. The evaluation of the chlorine contribution from such a heterogeneous collection of halogen compounds is clearly unsatisfactory; the individual variations may be due *inter alia* to real deviations attributable to the presence of more than one Cl atom on the same carbon atom. For Br and I, Sugden (*J.*, 1924, **125**, 1177) gives the values of 68·0 and 91·0, respectively, without disclosing how or from what data they are derived, whilst, for F, Allen and Sugden (*J.*, 1932, 760) deduce a value of 25·0 from measurements upon aromatic fluorine compounds. Eisenlohr (*Z. physikal. Chem.*, 1911, **75**, 585) utilises the data for 19 miscellaneous chloro-compounds for evaluating " Chlor in Chloriden ", 11 heterogeneous bromo-compounds for bromine, and 5 alkyl iodides for iodine. His results were :

	R_C.	R_D.	R_F.	$R_{G'}$.
Cl	5·933	5·967	6·043	6·101
Br	8·803	8·865	8·999	9·152
I	13·757	13·900	14·224	14·521

Apart from the obvious criticism as to the types of compound selected for Br and Cl, it must be remembered that the calculations are open to error because of the values for CH_2 employed (see Part IX, *J.*, 1946, 133).

The present author has deduced the constants for Cl by three independent methods: (1) From the experimental data for alkyl chlorides (Part VIII, *J.*, 1943, 636) and the aliphatic hydrocarbons (Parts IX and XI, *locc. cit.*). (2) From polymethylene dichlorides $Cl{\cdot}[CH_2]_n{\cdot}Cl$

TABLE I.

Parachors and refractivities for chlorine.

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	Mn_D^2
From alkyl chlorides and aliphatic hydrocarbons.						
Pr^nCl	56·2	5·86	5·88	5·96	6·01	49·78
Pr^iCl *	58·1	5·98	6·01	6·08	6·15	49·30
Bu^nCl	54·9	5·81	5·84	5·91	5·97	49·97
Bu^iCl	54·4	5·73	5·76	5·83	5·89	50·19
Bu^tCl *	58·3	6·06	6·09	6·17	6·22	49·12
Am^nCl	55·2	5·78	5·81	5·86	5·91	50·05
Am^iCl	55·7	5·88	5·91	5·98	6·04	50·00
$CHMePr^nCl$ *	58·7	6·07	6·11	6·19	6·25	49·25
$CHEt_2Cl$ *	60·9	6·20	6·23	6·33	6·37	49·17
$C_6H_{13}{}^nCl$	55·5	5·85	5·88	5·97	6·02	50·17
$C_7H_{15}{}^nCl$	55·3	5·76	5·78	5·86	5·90	50·22
$C_8H_{17}{}^nCl$	54·5	5·80	5·82	5·89	5·95	50·27
$C_9H_{19}{}^nCl$	56·0	5·83	5·86	5·93	5·96	50·51
$C_{10}H_{21}{}^nCl$	57·8	5·86	5·89	5·95	5·99	50·56
$C_{11}H_{22}{}^nCl$	57·0	5·79	5·84	5·90	5·95	50·61
$C_{12}H_{25}{}^nCl$	55·4	5·85	5·87	5·94	6·01	50·67
From polymethylene dichlorides, $Cl{\cdot}[CH_2]_n{\cdot}Cl$ and CH_2.						
$Cl{\cdot}[CH_2]_3{\cdot}Cl$	54·3	5·83	5·86	5·93	5·98	50·91
$Cl{\cdot}[CH_2]_5{\cdot}Cl$	54·7	5·76	5·78	5·85	5·90	50 97
From alkyl monochloroacetates and dialkyl succinates, $Cl{\cdot}CH_2{\cdot}CO_2R - 0{\cdot}5(CH_2{\cdot}CO_2R)_2$.						
$Cl{\cdot}CH_2{\cdot}CO_2Me$	53·7	5·82	5·84	5·92	5·96	50·60
$Cl{\cdot}CH_2{\cdot}CO_2Et$	54·3	5·88	5·91	5·98	6·03	50·56
$Cl{\cdot}CH_2{\cdot}CO_2Pr^n$	54·2	5·87	5·89	5·96	5·98	50·57
$Cl{\cdot}CH_2{\cdot}CO_2Bu^n$	54·2	5·82	5·85	5·91	5·96	50·68
Mean (excluding *)	55·2	5·821	5·844	5·918	5·973	50·41

and CH_2 (it is hoped to extend the series later). (3) From alkyl monochloroacetates, $Cl = Cl{\cdot}CH_2{\cdot}CO_2R - 0{\cdot}5(CH_2{\cdot}CO_2R)_2$; the experimental data for the dialkyl succinates are those given in Part XIII (preceding paper). The results are collected in Table I.

TABLE II.

Parachors and refractivities for bromine.

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
From alkyl bromides and aliphatic hydrocarbons.						
EtBr	69·5	8·67	8·73	8·89	9·01	116·55
Pr^{n}Br	68·4	8·66	8·72	8·87	8·99	117·26
Pr^{i}Br *	71·3	8·92	8·98	9·14	9·27	116·39
Bu^{n}Br	68·5	8·69	8·74	8·90	9·02	117·50
Bu^{i}Br	70·3	8·84	8·90	9·05	9·16	117·07
Bu^{s}Br *	72·3	9·09	9·15	9·31	9·45	116·65
Am^{n}Br	68·1	8·67	8·74	8·87	9·00	117·84
Am^{i}Br †	67·5	8·63	8·69	8·85	8·98	117·65
Am^{i}Br ‡	70·0	8·85	8·92	9·07	9·26	117·50
$CHMe_2Pr^nBr$ *	71·2	8·90	8·97	9·13	9·26	116·98
$CHEt_2Br$ *	73·2	9·08	9·14	9·32	9·44	117·06
$C_6H_{13}{}^nBr$	68·3	8·69	8·74	8·91	9·03	117·90
$C_7H_{15}{}^nBr$	67·8	8·65	8·71	8·86	8·98	118·05
$C_8H_{17}{}^nBr$	68·1	8·71	8·76	8·92	9·04	118·04
$C_9H_{19}{}^nBr$	69·1	8·61	8·67	8·80	8·90	118·48
$C_{10}H_{21}{}^nBr$	70·4	8·81	8·87	9·01	9·13	118·43
$C_{11}H_{23}{}^nBr$	68·8	8·58	8·65	8·80	8·91	118·63
$C_{12}H_{25}{}^nBr$	72·0	8·79	8·84	9·00	9·11	118·67
$C_{14}H_{25}{}^nBr$	69·2	8·59	8·64	8·79	8·90	118·92
$C_{16}H_{33}{}^nBr$	70·1	8·67	8·73	8·88	9·00	119·02
From polymethylene dibromides, $Br{\cdot}[CH_2]_n{\cdot}Br$ and CH_2.						
$Br{\cdot}[CH_2]_2{\cdot}Br$	67·6	8·77	8·84	9·00	9·12	123·98 *
$Br{\cdot}[CH_2]_3{\cdot}Br$	68·3	8·54	8·60	8·74	8·85	122·91 *
From alkyl monobromoacetates and dialkyl succinates, $Br{\cdot}CH_2{\cdot}CO_2R - 0{\cdot}5(CH_2{\cdot}CO_2R)_2$.						
$Br{\cdot}CH_2{\cdot}CO_2Pr^n$	67·1	8·68	8·74	8·89	8·99	118·71
$Br{\cdot}CH_2{\cdot}CO_2Bu^n$	66·1	8·52	8·58	8·72	8·84	118·87
Mean (excluding *)	68·8	8·681	8·741	8·892	9·011	118·07

† From Bisol fermentation *iso*amyl alcohol. ‡ From Sharples synthetic *iso*amyl alcohol.

TABLE III.

Parachors and refractivities for iodine.

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
From alkyl iodides and aliphatic hydrocarbons.						
MeI*	91·0	13·46	13·60	13·93	14·21	199·27
EtI	90·7	13·75	13·90	14·25	14·55	197·39
Pr^{n}I	90·7	13·83	13·97	14·32	14·62	196·67
Pr^{i}I *	92·1	14·20	14·35	14·73	15·01	195·93
Bu^{n}I	89·3	13·77	13·90	14·25	14·55	197·20
Bu^{i}I	90·9	13·80	13·94	14·28	14·58	195·75
Bu^{s}I *	95·4	14·38	14·53	14·91	15·24	195·67
Am^{n}I	90·1	13·85	13·98	14·32	14·62	197·60
Am^{i}I †	89·6	13·88	14·01	14·36	14·66	195·43
Am^{i}I ‡	91·7	13·86	14·00	14·35	14·65	195·58
$CHMePr^nI$ *	92·1	14·18	14·33	14·71	15·03	195·49
$CHEt_2I$ *	93·6	14·36	14·51	14·91	15·24	195·70
$C_6H_{13}{}^nI$	90·8	13·88	14·01	14·37	14·65	194·45
$C_7H_{15}{}^nI$	90·9	13·89	14·02	14·37	14·67	195·09
$C_8H_{15}{}^nI$	90·0	13·85	13·97	14·34	14·64	195·12
From $I{\cdot}[CH_2]_3{\cdot}I$ and CH_2.						
$I{\cdot}[CH_2]_3{\cdot}I$	88·6	13·66	13·79	14·14	—	212·05 *
From alkyl monoiodoacetates and dialkyl succinates, $I{\cdot}CH_2{\cdot}CO_2R - 0{\cdot}5(CH_2{\cdot}CO_2R)_2$.						
$I{\cdot}CH_2{\cdot}CO_2Pr^n$	91·1	13·77	13·89	14·25	14·53	197·39
$I{\cdot}CH_2{\cdot}CO_2Bu^n$	90·5	13·94	14·09	14·43	14·72	196·54
Mean (excluding *)	90·3	13·825	13·954	14·310	14·620	196·27

Refractivities refer to a temperature of 20°. In the calculation of the mean values, the figures for secondary alkyl chlorides (which give consistently high results) were omitted. The satisfactory agreement between the values deduced by the three entirely independent methods is noteworthy.

Analogous methods were employed in the calculation of the constants for Br; the experimental data for alkyl bromides (Part VIII, *loc. cit.*), to which have been added *n*-tetradecyl and *n*-hexadecyl bromides, were used. The results are summarised in Table II.

The results for I are collected in Table III: the data for alkyl iodides are those given in Part VIII (*loc. cit.*).

The results for the constants of F are not so satisfactory as those for the other halogens, chiefly because of the difficulty of preparing the pure alkyl fluorides in quantity. The figures are collected in Table IV and must be regarded as provisional. It will be noted that data for fluorobenzene, *p*-fluorotoluene, and α-fluoronaphthalene are included: the constants for Ph were deduced from PhCl, PhBr, and PhI; for *p*-$C_6H_4Me^-$ from *p*-$C_6H_4MeCl - Cl$; and for $C_{10}H_7{}^a$ from $C_{10}H_7{}^aCH_3 - CH_3$ (see following paper).

TABLE IV.

Preliminary values for the parachor and refractivities of fluorine.

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
$C_5H_{11}{}^nF$	26·6	0·74	0·74	0·71	0·70	21·89
$C_6H_{13}{}^nF$	27·0	0·83	0·82	0·82	0·81	21·72
$C_7H_{15}{}^nF$	25·0	0·72	0·72	0·70	0·70	21·81
$C_8H_{17}{}^nF$	25·6	0·93	0·93	0·93	0·92	21·94
C_6H_5F *	26·0	0·75	0·73	0·69	0·65	12·37
p-$CH_3{\cdot}C_6H_4F$ *	26·5	0·61	0·61	0·55	0·50	19·63
$C_{10}H_7{}^aF$ *	27·9	0·76	0·73	0·69	—	22·28
Mean (excluding *)	26·1	0·81	0·81	0·79	0·78	21·84

EXPERIMENTAL.

Ethylene Dichloride.—Method 1. A mixture of 62 g. of dry ethylene glycol, b. p. 196—196·5°/764 mm., and 158 g. of pure, dry pyridine was placed in a 500-ml. Claisen flask fitted with a double-surface condenser and a dropping-funnel: the side arm was closed with a cork. 480 G. of redistilled thionyl chloride were added slowly during 5 hours; a very vigorous reaction occurred and the liquid darkened considerably. The mixture was refluxed for 6 hours and then poured, with stirring, into ice-cold water. The dark heavy layer was separated, washed once with 5% sodium hydroxide solution, then twice with water and dried ($MgSO_4$). Upon distillation, pure ethylene dichloride (30 g.) passed over at 83°/756 mm.

Method 2. The pure commercial product (B.D.H.) was washed successively with saturated sodium hydrogen carbonate solution and water, dried ($MgSO_4$), and fractionated through a 3-section, Pyrex Young and Thomas column: about 95% passed over at 83°/748 mm. About 100 g. of this were distilled through a Widmer column and a middle fraction, b. p. 83°/762 mm., collected.

Propylene Dichloride.—A commercial sample was purified as for ethylene dichloride and distilled through an efficient fractionating column; b. p. 96°/770 mm.

Benzyl Chloride.—A pure commercial sample was twice redistilled from an all-glass apparatus; b. p. 177°/760 mm.

Trimethylene Dichloride.—76 G. of trimethylene glycol, b. p. 213—214°/758 mm., were placed in a 750-ml. round-bottomed Pyrex flask fitted with a dropping-funnel, a double-surface condenser, and a device for absorbing the hydrogen chloride evolved. 476 G. of redistilled thionyl chloride were added during 4 hours, and the mixture was refluxed for a further 4 hours. The reaction mixture was then distilled through an efficient column; the excess of thionyl chloride passed over at 76°, the temperature rose sharply to 116°, and the crude trimethylene dichloride (48 g.) was collected at 117—118°. This was washed and dried as above. Distillation gave pure trimethylene dichloride, b. p. 119—119·5°/756 mm.

Methyl Chloroacetate.—A mixture of 65 g. of A.R. monochloroacetic acid, 88 g. of pure absolute methyl alcohol, and 10 g. of concentrated sulphuric acid was refluxed for 7 hours, then poured into excess of water, and the lower layer separated. When purified as above, the ester (27 g.) boiled constantly at 129°/756 mm.

Ethyl Chloroacetate.—A mixture of 65 g. of A.R. monochloroacetic acid, 95 g. of absolute ethyl alcohol, and 11 g. of concentrated sulphuric acid was refluxed for 36 hours. This yielded, when worked up as above, 65 g. of pure ethyl chloroacetate, b. p. 142°/751 mm.

n-*Propyl Chloroacetate.*—A mixture of A.R. monochloroacetic acid, 115 g. of pure *n*-propyl alcohol, and 12 g. of concentrated sulphuric acid, refluxed for 30 hours, yielded by the above procedure 48 g. of *n*-propyl chloroacetate, b. p. 160—161°/764 mm.

n-*Butyl Chloroacetate.*—A mixture of 31·5 g. of A.R. monochloroacetic acid, 37 g. of pure *n*-butyl alcohol, 80 ml. of sodium-dried A.R. benzene, and 10 g. of concentrated sulphuric acid was refluxed for 30 hours, and then poured into excess of water. The benzene layer was washed with saturated sodium hydrogen carbonate solution and water, dried, and distilled. The yield of ester, b. p. 179—179·5°/766 mm., was 38 g.

Ethylene Dibromide.—To a mixture of 2500 g. of A.R. 48% hydrobromic acid and 750 g. of

concentrated sulphuric acid were added 372 g. of ethylene glycol, b. p. 196—196·5°/760 mm., followed by 1200 g. of concentrated sulphuric acid slowly. The mixture was refluxed for 11 hours and then distilled until no water-insoluble liquid passed over. The resulting crude dibromide (945 g.) was washed twice with an equal volume of concentrated hydrochloric acid, then successively with water, saturated sodium hydrogen carbonate solution, and water, and dried and distilled. The dibromide passed over constantly at 130·5°/758 mm.

Propylene Dibromide.—To a mixture of 2000 g. of A.R. 48% hydrobromic acid and 600 g. of concentrated sulphuric acid were added 367 g. of propylene glycol, b. p. 186—187°/749 mm., followed by 960 g. of concentrated sulphuric acid slowly. The mixture was refluxed gently for 10 hours: there was a considerable evolution of hydrogen bromide during the first 2 hours of heating and some charring (the quantity of concentrated sulphuric acid could be reduced with advantage). The bromide (457 g.) was distilled off directly from the reaction mixture and after purification, as for ethylene dibromide, yielded upon distillation 30 g. of a liquid, b. p. *ca.* 40°, and 400 g. of pure propylene dibromide, b. p. 141—142°/770 mm.

Trimethylene Dibromide.—This was prepared in the usual manner from trimethylene glycol, b. p. 213—214°/758 mm., and purified by washing with concentrated hydrochloric acid, etc., as above. It boiled constantly at 165—165·5°/759 mm.

n-*Propyl Bromoacetate.*—A mixture of 35 g. of bromoacetic acid (m. p. 50°), 24 g. of pure *n*-propyl alcohol, 95 ml. of sodium-dried A.R. benzene, and 8 g. of concentrated sulphuric acid was refluxed for 31 hours, then poured into excess of water, the benzene layer removed, washed with saturated sodium hydrogen carbonate solution and water, and dried and distilled. The yield of *n*-propyl bromoacetate, b. p. 175—177°/762, a slightly lachrymatory liquid (compare literature), was 30 g.

n-*Butyl Bromoacetate.*—A mixture of 35 g. of bromoacetic acid, 29 g. of pure *n*-butyl alcohol, 95 ml. of dry benzene, and 8 g. of concentrated sulphuric acid was refluxed for 31 hours and yielded, as for the *n*-propyl ester, 35 g. of *n*-butyl bromoacetate, b. p. 196—197°/760 mm.

Ethyl α-Bromopropionate.—In a 1500-ml. three-necked flask, equipped with a dropping-funnel, a double-surface condenser and a device for absorbing the sulphur dioxide evolved, were placed 440 g. of redistilled thionyl chloride, and the whole heated to boiling. 250 G. of pure propionic acid were added at such a rate that the mixture refluxed gently (1 hour). The mixture was then refluxed for 30 minutes to expel dissolved sulphur dioxide, allowed to cool, and 1 g. of purified red phosphorus added. 620 G. of dry bromine were then introduced during 7 hours to the gently boiling propionyl chloride; the mixture was then refluxed for 7 hours, by which time the evolution of hydrogen bromide had almost ceased. The crude α-bromopropionyl chloride was then introduced during 2·5 hours into 500 ml. of absolute ethyl alcohol contained in a three-necked flask equipped with a mechanical stirrer and reflux condenser: the reaction was completed by heating on a water-bath for 4 hours, hydrogen chloride being slowly evolved. The crude ester was filtered into 1 l. of distilled water, the oil separated and washed successively with water, sodium hydrogen carbonate solution and water, and then dried. Distillation gave about 150 g. of a low-b. p. fraction (largely ethyl bromide) and 442 g. of ethyl α-bromopropionate, b. p. 69—70°/25 mm. Redistillation yielded the pure ester, b. p. 71°/26 mm., as a colourless liquid, which was kept in the dark.

n-*Tetradecyl Bromide.*—*n*-Tetradecyl alcohol, m. p. 37·5—38° (Deutsche Hydrierwerke), was converted into the bromide by the hydrogen bromide procedure (*Org. Synth.*, 1935, **15**, 25); this boiled at 181°/21 mm. and had m. p. 5°. The red phosphorus–bromine procedure (Vogel, B.P. 565,452, 1944) gave an excellent yield of a product, b. p. 180°/20 mm., m. p. 5°, $d_4^{20°}$ 1·0169, $n_D^{20°}$ 1·46045.

n-*Hexadecyl Bromide.*—60 G. of *n*-hexadecyl alcohol, m. p. 48° (Deutsche Hydrierwerke), were warmed to 100—110° and treated with hydrogen bromide for 7 hours. The crude bromide was warmed to 25° and one-third of the volume of concentrated sulphuric acid was added; the ammonia–methanol purification procedure of *Org. Synth.* (*loc. cit.*) could not be applied because of the difficulty in dealing with the emulsions formed. The bromide was accordingly extracted with ether, washed with water, and dried ($CaSO_4$). Distillation yielded 51 g. of the pure bromide, b. p. 201°/19 mm., m. p. 14°.

2-*Phenylethyl Bromide.*—This was prepared from 2-phenylethyl alcohol, b. p. 216·5—217°/755 mm., purified red phosphorus, and A.R. bromine (Vogel, *loc. cit.*) and had b. p. 98°/12 mm.

2-*Ethoxyethyl Bromide.*—The reaction between 80 g. of A.R. bromine and a mixture of 100 g. of 2-ethoxyethyl alcohol, 15·5 g. of purified red phosphorus, and 3 g. of pure pyridine (Vogel, *loc. cit.*) gave, after the product had been washed with water, dried (K_2CO_3), and carefully fractionated, 28 g. of ethyl bromide and 32 g. of 2-ethoxyethyl bromide, b. p. 128°/768 mm.

Tetrahydrofurfuryl Bromide.—60 G. of A.R. bromine were added slowly to a boiling mixture of 76·5 g. of tetrahydrofurfuryl alcohol (b. p. 175·5—176°/762 mm.) and 11·6 g. of purified red phosphorus (B.P. 565,452, 1944); 5 g. of pure pyridine and 75 ml. of water were then added, and the mixture distilled. The crude bromide was separated, washed, dried, and distilled, first at normal pressure (b. p. 170°/755 mm.) and then under reduced pressure (b. p. 52°/4·8 mm.). The yield of colourless product was 35 g.

Trimethylene Di-iodide.—25·3 G. of trimethylene glycol, b. p. 213—214°/758 mm., and 440 g. of constant-b. p. hydriodic acid were distilled slowly (7 hours) from a 500-ml. Pyrex distilling flask. The crude di-iodide (96 g.) was separated from the distillate, and the acid layer was similarly distilled with a further 25·3 g. of trimethylene glycol, affording 84 g. more of the crude di-iodide. The combined products were washed with 10% sodium hydroxide solution and water, dried ($MgSO_4$), and then shaken mechanically with a little silver powder, which removed most of the colour. Upon distillation from a little silver powder, pure colourless trimethylene di-iodide passed over at 90·5°/9 mm.

The preparation by the red phosphorus–iodine method (Vogel, *loc. cit.*) gave a product of b. p. 88—89°/6 mm., $d_4^{20°}$ 2·5702, $n_D^{20°}$ 1·6471.

2-*Phenylethyl Iodide.*—This was prepared by the red phosphorus–iodine procedure from 2-phenylethyl alcohol (b. p. 216·5—217°/755 mm.) and boiled at 114—116°/12 mm. Upon redistillation most of it passed over at 116°/12 mm. and was a perfectly colourless liquid.

n-*Propyl Iodoacetate.*—A mixture of 41·5 g. of pure monoiodoacetic acid, m. p. 82°, 24 g. of pure *n*-propyl alcohol, 95 ml. of sodium-dried A.R. benzene, and 8 g. of concentrated sulphuric acid was

refluxed for 30 hours and then poured into excess of water. The lower layer was separated, washed with saturated sodium hydrogen carbonate solution and water, dried, and distilled from a little silver powder. The yield of crude ester, b. p. 197·5—198·5°/760 mm., was 39 g. This was slightly coloured and the pale red colour could be removed by shaking with a little silver powder but not by distillation from it at atmospheric pressure. Distillation under reduced pressure from silver powder gave the pure, colourless ester, b. p. 72°/7 mm.

n-*Butyl Iodoacetate.*—A mixture of 41·5 g. of pure iodoacetic acid, 29 g. of pure *n*-butyl alcohol, 95 ml. of sodium-dried A.R. benzene, and 8 g. of concentrated sulphuric acid was refluxed for 30 hours and yielded, as for the *n*-propyl ester, 44 g. of n-*butyl iodoacetate*, b. p. 214—216°/765 mm., which, however, was coloured deep red. The colour was removed by allowing it to stand over silver powder for 2 days: it was then distilled from a little silver powder and had b. p. 86°/7 mm. (Found: C, 29·7; H, 4·6; I, 52·7. $C_6H_{11}O_2I$ requires C, 29·8; H, 4·6; I, 52·4%).

Alkyl Fluorides.—The alkyl fluorides were prepared by the action of mercurous fluoride upon the corresponding alkyl bromide by a modification of the method of Swarts (*Bull. Acad. roy. Belg.*, 1921, **7**, 438); the addition of a little iodine, as suggested by Desreux (*ibid.*, 1934, **20**, 47; *Bull. Soc. chim. Belg.*, 1935, **44**, 1), was not advantageous except for *n*-amyl and *n*-hexyl fluorides. Contrary to the experience of the latter author, no secondary alkyl fluorides appeared to be formed in the reactions: the yields were uniformly poor. In all cases, the ethylenic hydrocarbon was a by-product.

Mercurous fluoride. Commercial mercurous fluoride gave a negligible yield of alkyl fluoride. Mercurous fluoride was accordingly prepared as follows. To a solution of 281 g. of A.R. mercurous nitrate in 5 l. of water and 35 ml. of concentrated hydrochloric acid was slowly added with vigorous mechanical stirring a solution of 125 g. of pure potassium hydrogen carbonate in 300 ml. of water. The resulting yellow precipitate was kept in the dark for 3 days with occasional stirring to decompose any basic nitrate. The mercurous carbonate was filtered off and washed successively with water, methyl alcohol, and ether: after drying in a vacuum desiccator over anhydrous calcium chloride the yield was 240 g. This mercurous carbonate was added in small portions to exceess of A.R. 40% hydrofluoric acid contained in a beaker coated inside with a layer of wax. The resulting yellow precipitate was washed with a *little* water by decantation, filtered off, and dried in a vacuum desiccator over anhydrous calcium chloride. The yield of mercurous fluoride was 188 g.

n-*Amyl fluoride.* An intimate mixture of 164 g. of dry mercurous fluoride, 108 g. of *n*-amyl fluoride, and 3 g. of iodine, contained in a copper flask fitted with a screw-on copper still-head to which were attached a double-surface condenser and a receiver cooled in ice, was heated in a bath at 115—118° for 9 hours: 12 g. of distillate were collected. After standing overnight, heating was continued at 135—140° for 3 hours, and a further 32 g. of liquid was collected. The combined distillates were treated with water and a little calcium chloride (to facilitate separation of the upper organic layer). Small volumes of saturated sodium hydrogen carbonate solution were added to the upper layer until reaction ceased, the silica was filtered off, and the liquid dried and fractionated: this gave fractions of b. p. 50—80° (12 g.) and 80—128° (12 g.). The latter was returned to the flask and yielded a further small quantity of crude *n*-amyl fluoride upon heating at 115—120° for 4 hours. The fraction of b. p. 50—80° (crude *n*-amyl fluoride + amylene) was cooled in ice and titrated with a solution of bromine in potassium bromide solution (90 g. Br_2; 60 g. KBr in 500 ml. of water) until a slight excess of bromine was present. The lower layer was removed, washed with potassium bromide solution until colourless, then with water, and dried ($MgSO_4$). Fractional distillation then gave 4 g. of *n*-amyl fluoride, b. p. 62—63°/767 mm.

n-*Hexyl fluoride.* An intimate mixture of 145 g. of mercurous fluoride, 101 g. of *n*-hexyl bromide, and 2·5 g. of iodine was heated, as for *n*-amyl fluoride, at 140—150° for 16 hours and at 160° for 8 hours. The distillate (49 g.) was diluted with water, treated with saturated sodium hydrogen carbonate solution then water, filtered from the silica, and the upper layer separated, dried, and fractionated: two fractions were collected of b. p. 80—140° (10 g.) and 140—155° (18 g.) respectively. The latter was mixed with 72·5 g. of mercurous fluoride, 3 g. of iodine, and 60·5 g. of *n*-hexyl bromide, and heated in a bath at 120—130° for 12 hours, 130—150° for 24 hours, and 150—155° for 12 hours. The distillate (combined with the fraction of b. p. 80—140° from the first distillation) was largely diluted with water, the upper organic layer (15 g.) removed, washed with saturated sodium hydrogen carbonate solution then water, dried, and distilled. This gave 12 g. of liquid, b. p. 80—100°, and consisted of a mixture of *n*-hexyl fluoride and hexene. The latter was removed by titration with bromine in potassium bromide solution as before and the product afforded, after two fractionations, 4 g. of *n*-hexyl fluoride, b. p. 88°/765 mm.

n-*Heptyl fluoride.* A mixture of 82·5 g. of *n*-heptyl bromide (VIII, **79**) and 110 g. of mercurous fluoride in a copper flask was heated, as for *n*-amyl fluoride, at 100° for 3 hours; the temperature was raised to 140° during 6 hours and finally to 160° during 3 hours. The upper layer (22 g.) of the distillate was removed, washed with saturated sodium hydrogen carbonate solution and water, dried, and fractionated. The liquid of b. p. 102—130° (13 g.) was freed from unsaturated hydrocarbons by means of bromine in potassium bromide solution as before, and upon distillation gave 8 g. of crude *n*-heptyl fluoride, b. p. 115—122°, the dibromoheptane remaining in the flask as a dark oil. Redistillation afforded 6 g. of the pure fluoride, b. p. 117°/779 mm.

n-*Octyl fluoride.* A mixture of 90 g. of *n*-octyl bromide (VIII, **80**) and 128 g. of mercurous fluoride was gradually heated, as before, to 150°, kept at this temperature for 2 hours and then at 150—190° for 6 hours. The distillate was poured into excess of water, the pale yellow upper layer (32 g.) removed, washed with sodium hydrogen carbonate solution and water, and the residual 26 g. of organic liquid were titrated directly without previous distillation, with bromine in potassium bromide solution, washed, dried, and distilled. 14 G. of liquid were collected at 140—145°/760 mm. (mainly at 142—143°), fuming (due to hydrogen bromide) then commenced, and a liquid passed over at 145—165° which contained little octyl fluoride. The liquid, b. p. 140—145°, after treatment with anhydrous potassium carbonate, distilled at 142—143°/760 mm.

Fluorobenzene. This was prepared from phenyldiazonium chloride (*ex* A.R. aniline) and fluoboric acid in wax-coated vessels according to *Org. Synth.*, 1933, **13**, 46 (compare Balz and Schiemann, *Ber.*,

1927, **60**, 1188), and boiled constantly at 84·5°/760 mm. Subsequently it was found that the fluoboric acid could be replaced by sodium borofluoride in this and other preparations of aromatic fluorine compounds.

p-*Fluorotoluene.* This was prepared from pure *p*-toluidine and boiled constantly at 115·5°/756 mm.

α-*Fluoronaphthalene.* 71·5 G. of pure α-naphthylamine were dissolved in 174 g. of concentrated hydrochloric acid contained in a 1-l. three-necked flask, fitted with a mechanical stirrer and dropping-funnel, and cooled in ice. A cold solution of 37·5 g. of pure sodium nitrite in 47 ml. of water was added slowly to an end-point with starch–iodide paper, the temperature being kept below 7° throughout. A solution of fluoboric acid (from 17·6 of pure boric anhydride and 101 g. of A.R. 40% hydrofluoric acid contained in a Bakelite beaker) was poured into the well-stirred diazonium salt solution at such a rate that the temperature did not rise above 10°. Stirring was continued for 60 minutes, and the precipitated borofluoride filtered off at the pump, washed with 25 ml. of ice-cold water, 25 ml. of methyl alcohol, and 25 ml. of ether, then dried between absorbent filter-paper for 12 hours and in a vacuum desiccator over anhydrous calcium chloride for several days. The resulting α-naphthyldiazonium fluoborate (82 g.) was decomposed in 20-g. lots in the usual manner and afforded, after dissolution in ether and washing with 10% sodium hydroxide solution, etc., a 90% yield of α-fluoronaphthalene, b. p. 214°/758 mm. For the physical measurements this was redistilled and a middle fraction, b. p. 98°/17 mm., taken.

p-*Chlorotoluene.* This was prepared from pure *p*-toluidine (*Org. Synth.*, 1923, **3**, 33) and boiled at 161·5°/769 mm.

m-*Dichlorobenzene.* The pure commercial product was washed successively with 10% sodium hydroxide solution and then with water until the washings were neutral, dried ($MgSO_4$), and distilled in an all-glass apparatus. It boiled constantly at 172·5°/760 mm. The compound attacks rubber corks.

Benzenesulphonyl fluoride. Benzenesulphonyl chloride, b. p. 247°/757 mm., was refluxed with aqueous potassium fluoride solution for 90 minutes (Davies, *J.*, 1931, 2104) and allowed to stand for 12 hours; 100 ml. of water were then added, and the fluoride extracted with 100 ml. of ether, the extract dried, the solvent removed, and the residue twice fractionated from an all-glass apparatus; b. p. 208—209°/753 mm.; yield 30 g.

Benzenesulphonyl chloride. A commercial product was first distilled from an all-glass apparatus, and the fraction, b. p. 247°/757 mm., collected. This was redistilled from an all-glass apparatus and had b. p. 135°/25 mm.

279. *Ethylene dichloride.* B. p. 83°/762 mm.; M 98·97; n_C 1·44252, n_D 1·44485, n_F 1·45076, $n_{G'}$ 1·45506; R_C 20·91, R_D 21·00, R_F 21·24, $R_{G'}$ 21·42; $Mn_D^{20°}$ 143·00. Densities determined: $d_{4°}^{20°}$ 1·2538, $d_{4°}^{41·4°}$ 1·2234, $d_{4°}^{60·5°}$ 1·1968. Apparatus *D*.

(These headings apply to corresponding columns in all the following tables.)

t.	*H.*	$d_{4°}^{t°}$.	γ.	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	γ.	*P.*
13·7°	10·74	1·2627	33·49	188·6	41·4°	9·76	1·2234	29·49	188·7
18·4	10·57	1·2561	32·79	188·5	61·5	9·03	1·1954	26·66	188·4
								Mean	188·6

Another sample, prepared by the thionyl chloride–pyridine method, had b. p. 83°/756 mm., $d_{4°}^{20°}$ 1·2540, n_C 1·44254, n_D 1·44495, n_F 1·45088, $n_{G'}$ 1·45519.

280. *Propylene dichloride.* B. p. 96°/770 mm.; M 113·00; n_C 1·43693, n_D 1·43928, n_F 1·44510, $n_{G'}$ 1·44931; R_C 25·56, R_D 25·69, R_F 26·04, $R_{G'}$ 26·19; $Mn_D^{20°}$ 144·95. Densities determined: $d_{4°}^{20°}$ 1·1578, $d_{4°}^{42·1°}$ 1·1294, $d_{4°}^{61·5°}$ 1·1046. Apparatus *D*.

14·9°	10·27	1·1644	29·53	226·2	41·4°	9·41	1·1303	26·27	226·4
17·1	10·22	1·1615	29·32	226·4	62·3	8·70	1·1036	23·71	226·2
24·8	9·97	1·1516	28·35	226·4				Mean	226·3

281. *Benzyl chloride.* B. p. 177°/760 mm.; M 126·59; n_C 1·53398, n_D 1·53887, n_F 1·55142, $n_{G'}$ 1·56134; R_C 35·76, R_D 36·03, R_F 36·72, $R_{G'}$ 37·27; $Mn_D^{20°}$ 194·81. Densities determined: $d_{4°}^{20°}$ 1·1004, $d_{4°}^{40·7°}$ 1·0806, $d_{4°}^{60·5°}$ 1·0621, $d_{4°}^{86·8°}$ 1·0372. Apparatus *A*.

20·6°	18·19	1·0998	37·46	284·8	62·2°	16·22	1·0605	32·21	284·4
26·3	17·94	1·0944	36·76	284·8	88·5	15·03	1·0356	29·15	284·0
41·2	17·16	1·0801	34·71	284·5				Mean	284·5

282. *Trimethylene dichloride.* B. p. 119·5°/756 mm.; M 113·00; n_C 1·44632, n_D 1·44871, n_F 1·45455, $n_{G'}$ 1·45883; R_C 25·39, R_D 25·50, R_F 25·79, $R_{G'}$ 26·00; $Mn_D^{20°}$ 163·70. Densities determined: $d_{4°}^{20°}$ 1·1878, $d_{4°}^{41·5°}$ 1·1615, $d_{4°}^{61·7°}$ 1·1382, $d_{4°}^{86·2°}$ 1·1050. Apparatus *A*.

15·7°	15·42	1·1930	34·45	229·5	60·9°	13·37	1·1392	28·52	229·2
19·0	15·26	1·1890	33·97	229·5	87·4	12·21	1·1043	25·25	229·4
41·6	14·24	1·1614	30·97	229·5				Mean	229·4

283. *Methyl chloroacetate.* B. p. 129°/756 mm.; M 108·53; n_C 1·41976, n_D 1·42196, n_F 1·42716, $n_{G'}$ 1·43104; R_C 22·24, R_D 22·34, R_F 22·59, $R_{G'}$ 22·76; $Mn_D^{20°}$ 154·33. Densities determined: $d_{4°}^{20°}$ 1·2343, $d_{4°}^{41·1°}$ 1·2072, $d_{4°}^{60·8°}$ 1·1809, $d_{4°}^{86·5°}$ 1·1463. Apparatus *A*.

12·8°	15·56	1·2437	36·24	214·1	41·2°	14·31	1·2071	32·34	214·4
18·1	15·33	1·2368	35·50	214·2	63·0	13·40	1·1780	29·56	214·9
24·9	15·17	1·2279	34·88	214·8	86·2	12·47	1·1471	26·78	215·4
								Mean	214·6

284. *Ethyl chloroacetate.* B. p. 142°/751 mm.; M 122·56; n_C 1·41933, n_D 1·42151, n_F 1·42675, $n_{G'}$ 1·43055; R_C 26·94, R_D 27·06, R_F 27·36, $R_{G'}$ 27·57; $Mn_D^{20°}$ 174·22. Densities determined: $d_4^{20°}$ 1·1498, $d_4^{49·7°}$ 1·1248, $d_4^{61·6°}$ 1·0995, $d_4^{86·2°}$ 1·0684. Apparatus *D*.

t.	H.	$d_{4°}^{t°}$.	γ.	P.	t.	H.	$d_{4°}^{t°}$.	γ.	P.
21·4°	11·18	1·1481	31·70	253·3	61·9°	9·86	1·0991	26·76	253·6
25·9	11·05	1·1426	31·18	253·5	86·8	9·12	1·0677	24·05	254·2
41·5	10·54	1·1238	29·25	253·6				Mean	253·6

285. n-*Propyl chloroacetate.* B. p. 161°/764 mm.; M 136·58; n_C 1·42327, n_D 1·42546, n_F 1·43074, $n_{G'}$ 1·43432; R_C 31·58, R_D 31·72, R_F 32·06, $R_{G'}$ 32·29; $Mn_D^{20°}$ 194·69. Densities determined: $d_4^{20°}$ 1·1020, $d_4^{41·3°}$ 1·0791, $d_4^{61·4°}$ 1·0558, $d_4^{85·3°}$ 1·0275. Apparatus *A*.

14·6°	15·12	1·1080	31·37	291·7	41·3°	14·00	1·0791	28·29	291·9
20·2	14·89	1·1018	30·72	291·8	61·4	13·23	1·0558	26·15	292·6
25·0	14·77	1·0964	30·32	292·3	86·1	12·32	1·0266	23·68	293·5
								Mean	292·3

286. n-*Butyl chloroacetate.* B. p. 179·5°/766 mm.; M 150·61; n_C 1·42746, n_D 1·42967, n_F 1·43505, $n_{G'}$ 1·43887; R_C 36·14, R_D 36·30, R_F 36·69, $R_{G'}$ 36·97; $Mn_D^{20°}$ 215·33. Densities determined: $d_4^{20°}$ 1·0713, $d_4^{40·8°}$ 1·0492, $d_4^{61·9°}$ 1·0262, $d_4^{86·7°}$ 0·9989. Apparatus *D*.

19·3°	11·49	1·0720	30·42	330·8	62·2°	10·26	1·0259	25·99	332·3
23·9	11·46	1·0670	30·20	331·7	86·7	9·58	0·9989	23·63	333·3
42·0	10·81	1·0479	27·98	331·3				Mean	331·9

287. *Ethylene dibromide.* B. p. 130·5°/758 mm.; M 187·89; n_C 1·53491, n_D 1·53891, n_F 1·54899, $n_{G'}$ 1·55690; R_C 26·79, R_D 26·96, R_F 27·38, $R_{G'}$ 27·70; $Mn_D^{20°}$ 289·14. Densities determined: $d_4^{20°}$ 2·1829, $d_4^{41·6°}$ 2·1388, $d_4^{64·8°}$ 2·0915, $d_4^{85·8°}$ 2·0469. Apparatus *A*.

13·7°	9·67	2·1959	39·76	214·9	62·0°	8·46	2·0972	33·22	215·1
24·3	9·47	2·1741	38·56	215·3	87·5	7·85	2·0432	30·03	215·4
41·4	8·99	2·1392	36·01	215·2				Mean	215·2

288. *Propylene dibromide.* B. p. 141·5°/770 mm.; M 201·92; n_C 1·51631, n_D 1·52006, n_F 1·52956, $n_{G'}$ 1·53668; R_C 31·58, R_D 31·77, R_F 32·26, $R_{G'}$ 32·62; $Mn_D^{20°}$ 306·94. Densities determined: $d_4^{20°}$ 1·9324, $d_4^{41·9°}$ 1·8958, $d_4^{62·1°}$ 1·8602, $d_4^{87·1°}$ 1·8139. Apparatus *A*.

20·7°	9·52	1·9312	34·43	253·3	61·3°	8·52	1·8616	29·70	253·2
42·5	8·99	1·8948	31·90	253·3	88·3	7·85	1·8118	26·63	253·2
								Mean	253·3

289. *Trimethylene dibromide.* B. p. 165°/759 mm.; M 201·92; n_C 1·51973, n_D 1·52330, n_F 1·53209, $n_{G'}$ 1·53880; R_C 30·95, R_D 31·13, R_F 31·57, $R_{G'}$ 31·90; $Mn_D^{20°}$ 307·59. Densities determined: $d_4^{20°}$ 1·9822, $d_4^{42·3°}$ 1·9444, $d_4^{69·8°}$ 1·9128, $d_4^{86·7°}$ 1·8662. Apparatus *D*.

12·3°	8·36	1·9954	41·20	256·4	62·0°	7·35	1·9102	34·67	256·5
22·1	8·17	1·9786	39·92	256·5	87·4	6·84	1·8650	31·50	256·5
42·4	7·79	1·9442	37·40	256·8				Mean	256·5

290. n-*Propyl bromoacetate.* B. p. 176°/762 mm.; M 181·04; n_C 1·44914, n_D 1·45177, n_F 1·45814, $n_{G'}$ 1·46288, $n_{G'}$ 1·46288; R_C 34·39, R_D 34·57, R_F 34·99, $R_{G'}$ 35·30; $Mn_D^{20°}$ 262·83. Densities determined: $d_4^{20°}$ 1·4122, $d_4^{41·6°}$ 1·3849, $d_4^{61·6°}$ 1·3588, $d_4^{86·7°}$ 1·3228. Apparatus *A*.

19·2°	12·13	1·4132	32·10	304·9	61·6°	10·77	1·3580	27·39	305·0
26·4	11·91	1·4039	31·31	305·0	87·3	10·08	1·3220	24·95	306·1
41·5	11·45	1·3848	29·69	305·2				Mean	305·2

291. n-*Butyl bromoacetate.* B. p. 196°/760 mm.; M 195·07; n_C 1·45078, n_D 1·45337, n_F 1·45969, $n_{G'}$ 1·46439; R_C 38·84, R_D 39·03, R_F 39·50, $R_{G'}$ 39·85; $Mn_D^{20°}$ 283·52. Densities determined: $d_4^{20°}$ 1·3519, $d_4^{41·5°}$ 1·3252, $d_4^{62·4°}$ 1·2992, $d_4^{86·4°}$ 1·2687. Apparatus *D*.

21·0°	9·50	1·3506	31·69	342·6	62·4°	8·64	1·2992	27·72	344·5
26·2	9·43	1·3441	31·30	343·3	87·3	8·04	1·2671	25·16	344·8
41·8	9·09	1·3246	29·74	343·9				Mean	343·8

292. *Ethyl α-bromopropionate.* B. p. 71°/26 mm.; M 181·04; n_C 1·44629, n_D 1·44896, n_F 1·45551, $n_{G'}$ 1·46029; R_C 34·17, R_D 34·35, R_F 34·78, $R_{G'}$ 35·10; $Mn_D^{20°}$ 262·33. Densities determined: $d_4^{20°}$ 1·4135, $d_4^{41·5°}$ 1·3843, $d_4^{59·7°}$ 1·3578, $d_4^{87·0°}$ 1·3200. Apparatus *D*.

25·9°	8·56	1·4053	29·71	300·8	60·7°	7·75	1·3564	25·97	301·1
28·9	8·51	1·4011	29·45	301·0	86·6	7·14	1·3206	23·29	301·1
40·8	8·23	1·3853	28·16	301·0				Mean	301·0

293. n-*Tetradecyl bromide.* B. p. 181°/21 mm., m. p. 5°; M 277·29; n_C 1·45794, n_D 1·46050, n_F 1·46661, $n_{G'}$ 1·47120; R_C 74·35, R_D 74·71, R_F 75·56, $R_{G'}$ 76·20; $Mn_D^{20°}$ 404·98. Densities determined: $d_{4°}^{20°}$ 1·0175, $d_{4°}^{40·0°}$ 1·0018, $d_{4°}^{66·1°}$ 0·9852, $d_{4°}^{86·20}$ 0·9638. Apparatus *A*.

t.	*H.*	$d_{4°}^{t°}$	γ.	*P.*	*t.*	*H.*	$d_{4°}^{t°}$	γ.	*P.*
17·2°	16·50	1·0197	31·50	644·3	58·3°	15·05	0·9866	27·80	645·4
19·3	16·40	1·0181	31·26	644·0	86·3	14·08	0·9637	25·41	645·9
40·0	15·60	1·0018	29·26	643·8				Mean	644·9

294. n-*Hexadecyl bromide.* B. p. 201°/19 mm., m. p. 14°; M 305·34; n_C 1·45980, n_D 1·46205, n_F 1·46812, $n_{G'}$ 1·47269; R_C 83·56, R_D 83·97, R_F 84·91, $R_{G'}$ 85·62; $Mn_D^{20°}$ 446·44. Densities determined: $d_{4°}^{20°}$ 0·9998, $d_{4°}^{40·2°}$ 0·9841, $d_{4°}^{59·5°}$ 0·9687, $d_{4°}^{86·1°}$ 0·9477. Apparatus *A*.

18·3°	16·95	1·0012	31·78	724·1	61·4°	15·46	0·9671	28·00	726·2
25·3	16·76	0·9956	31·25	725·1	87·3	14·61	0·9467	25·90	727·6
41·5	16·18	0·9831	29·78	725·6				Mean	725·7

295. 2-*Phenylethyl bromide.* B. p. 98°/12 mm.; M 185·07; n_C 1·55124, n_D 1·55635, n_F 1·56894, $n_{G'}$ 1·57899; R_C 43·47, R_D 43·81, R_F 44·62, $R_{G'}$ 45·27; $Mn_D^{20°}$ 288·04. Densities determined: $d_{4°}^{20°}$ 1·3587, $d_{4°}^{41·2°}$ 1·3360, $d_{4°}^{61·1°}$ 1·3148, $d_{4°}^{85·7°}$ 1·2881. Apparatus *A*.

16·3°	15·37	1·3627	39·23	339·9	41·1°	14·66	1·3361	36·68	340·9
20·9	15·30	1·3577	38·90	340·4	60·9	13·97	1·3150	34·40	340·8
27·2	15·07	1·3510	38·12	340·4	87·0	13·08	1·2865	31·51	340·8
								Mean	340·5

296. 2-*Ethoxyethyl bromide.* B. p. 128°/768 mm.; M 153·03; n_C 1·44590, n_D 1·44856, n_F 1·45513, $n_{G'}$ 1·46007; R_C 29·26, R_D 29·41, R_F 29·78, $R_{G'}$ 30·06; $Mn_{4°}^{20°}$ 221·68. Densities determined: $d_{4°}^{20°}$ 1·3944, $d_{4°}^{40·7°}$ 1·3649, $d_{4°}^{61·0°}$ 1·3343, $d_{4°}^{85·6°}$ 1·2943. Apparatus *D*.

15·6°	8·75	1·4010	30·27	256·2	41·0°	8·13	1·3645	27·40	256·6
21·1	8·58	1·3928	29·51	256·1	61·0	7·60	1·3343	25·04	256·6
27·1	8·47	1·3841	28·94	256·5	87·2	6·92	1·2963	22·15	256·1
								Mean	256·3

297. *Tetrahydrofurfuryl bromide.* B. p. 170°/755 mm. and 52°/4·8 mm.; M 165·04; n_C 1·48524, n_D 1·48811, n_F 1·49516, $n_{G'}$ 1·50057; R_C 32·31, R_D 32·40, R_F 32·80, $R_{G'}$ 33·10; $Mn_D^{20°}$ 245·60. Densities determined: $d_{4°}^{20°}$ 1·4679, $d_{4°}^{41·8°}$ 1·4397, $d_{4°}^{60·8°}$ 1·4155, $d_{4°}^{86·9°}$ 1·3823. Apparatus *A*.

17·8°	13·59	1·4708	37·43	277·5	40·2°	12·87	1·4415	34·74	278·0
19·3	13·52	1·4688	37·18	277·5	60·3	12·23	1·4162	32·43	278·1
24·1	13·36	1·4626	36·59	277·5				Mean	277·7

298. *Trimethylene di-iodide.* B. p. 90·5°/9 mm.; M 295·92; n_C 1·63579, n_D 1·64230, n_F 1·65893; R_C 41·18, R_D 41·51, $x_{G'}$ R_F 42·36; $Mn_D^{20°}$ 485·99. Densities determined: $d_{4°}^{20°}$ 2·5755, $d_{4°}^{41·3°}$ 2·5356, $d_{4°}^{60·6°}$ 2·4986, $d_{4°}^{88·0°}$ 2·4489. Apparatus *D*.

19·9°	6·92	2·5757	44·02	295·9	62·2°	6·44	2·4956	39·69	297·6
41·9	6·61	2·5345	41·37	296·1	87·3	6·30	2·4464	38·06	299·0
								Mean	297·2

This compound does not appear to wet glass well; the surface tension results may therefore be somewhat low.

299. 2-*Phenylethyl iodide.* B. p. 116°/12 mm.; M 232·07; n_C 1·59599, n_D 1·60216, n_F 1·61802, $n_{G'}$ 1·63095; R_C 48·38, R_D 48·78, R_F 49·81, $R_{G'}$ 50·65; $Mn_D^{20°}$ 371·82. Densities determined: $d_{4°}^{20°}$ 1·6323, $d_{4°}^{40·2°}$ 1·6087, $d_{4°}^{59·9°}$ 1·5845, $d_{4°}^{85·5°}$ 1·5528. Apparatus *A*.

14·4°	13·46	1·6390	41·31	359·0	61·2°	12·22	1·5829	36·22	359·7
19·0	13·28	1·6335	40·62	358·8	86·2	11·56	1·5520	33·59	360·0
42·2	12·85	1·6063	38·65	360·2				Mean	359·5

300. n-*Propyl iodoacetate.* B. p. 72°/7 mm.; M 228·04; n_C 1·49395, n_D 1·49762, n_F 1·50690, $n_{G'}$ 1·51425; R_C 39·48, R_D 39·72, R_F 40·35, $R_{G'}$ 40·84; $Mn_D^{20°}$ 341·51. Densities determined: $d_{4°}^{20°}$ 1·6817, $d_{4°}^{41·3°}$ 1·6490, $d_{4°}^{61·2°}$ 1·6193, $d_{4°}^{86·0°}$ 1·5816. Apparatus *D*.

17·4°	8·35	1·6857	34·76	328·5	62·1°	7·46	1·6179	29·81	329·3
24·3	8·26	1·6752	34·17	329·1	87·1	7·03	1·5799	27·43	330·3
42·1	7·82	1·6478	31·82	328·7				Mean	329·3

301. n-*Butyl iodoacetate.* B. p. 86°/7 mm.; M 242·07; n_C 1·48860, n_D 1·49213, n_F 1·50093, $n_{G'}$ 1·50782; R_C 44·26, R_D 44·54, R_F 45·21, $R_{G'}$ 45·73; $M_D^{20°}$ 361·19. Densities determined: $d_{4°}^{20°}$ 1·5773, $d_{4°}^{41·1°}$ 1·5507, $d_{4°}^{61·0°}$ 1·5255, $d_{4°}^{87·0°}$ 1·4958. Apparatus *D*.

21·8°	8·46	1·5750	32·91	368·1	61·4°	7·72	1·5251	29·08	368·6
28·3	8·40	1·5669	32·50	368·9	87·0	7·25	1·4958	26·78	368·2
41·5	8·05	1·5502	30·82	367·9				Mean	368·2

302. n-*Amyl fluoride.* B. p. 62—63°/767 mm.; M 90·14; n_C 1·35564, n_D 1·35725, n_F 1·36122, $n_{G'}$ 1·36392; R_C 24·88, R_D 24·99, R_F 25·23, $R_{G'}$ 25·40; $Mn_D^{20°}$ 122·35. Densities determined: $d_{4°}^{20°}$ 0·7909, $d_{4°}^{40·6°}$ 0·7663. Apparatus *D*.

t.	H.	$d_{4°}^{t°}$	γ.	P.	t.	H.	$d_{4°}^{t°}$	γ.	P.
15·4°	10·50	0·7964	20·65	241·5	24·8°	10·07	0·7851	19·52	241·6
17·5	10·37	0·7939	20·33	241·3	41·3	9·27	0·7655	17·61	241·4
22·6	10·26	0·7878	19·96	242·0				Mean	241·6

303. n-*Hexyl fluoride.* B. p. 88°/765 mm.; M 104·16; n_C 1·36939, n_D 1·37118, n_F 1·37544, $n_{G'}$ 1·37835; R_C 29·56, R_D 29·68, R_F 29·98, $R_{G'}$ 30·20; $Mn_D^{20°}$ 142·82. Densities determined: $d_{4°}^{20°}$ 0·7960, $d_{4°}^{41·0°}$ 0·7745, $d_{4°}^{60·2°}$ 0·7548. Apparatus *D*.

16·9°	11·02	0·7992	21·75	281·5	61·5°	9·29	0·7535	17·29	282·5
41·5	10·04	0·7740	19·19	282·0				Mean	282·0

304. n-*Heptyl fluoride.* B. p. 117°/779 mm.; M 118·19; n_C 1·38211, n_D 1·38394, n_F 1·38822, $n_{G'}$ 1·39154; R_C 34·12, R_D 34·27, R_F 34·61, $R_{G'}$ 34·87; $Mn_D^{20°}$ 163·56. Densities determined: $d_{4°}^{20°}$ 0·8063, $d_{4°}^{42·2°}$ 0·7841, $d_{4°}^{58·5°}$ 0·7678. Apparatus *D*.

16·9°	11·54	0·8094	23·07	320·1	42·2°	10·48	0·7841	20·77	321·8
23·2	11·33	0·8031	22·47	320·4	61·0	9·78	0·7652	18·48	320·3
								Mean	320·7

305. n-*Octyl fluoride.* B. p. 142·5°/760 mm.; M 132·22; n_C 1·39244, n_D 1·39345, n_F 1·39898, $n_{G'}$ 1·40220; R_C 38·89, R_D 39·07, R_F 39·47, $R_{G'}$ 39·75; $Mn_D^{20°}$ 184·37. Densities determined: $d_{4°}^{20°}$ 0·8103, $d_{4°}^{41·3°}$ 0·7926, $d_{4°}^{61·1°}$ 0·7747, $d_{4°}^{86·9°}$ 0·7518. Apparatus *A*.

17·7°	15·98	0·8123	24·31	361·4	43·0°	14·72	0·7911	21·81	361·2
20·4	15·77	0·8100	23·92	361·0	62·3	13·80	0·7737	19·99	361·4
26·9	15·61	0·8044	23·51	361·9	87·9	12·59	0·7509	17·70	361·2
								Mean	361·3

306. *Fluorobenzene.* B. p. 84·5°/760 mm.; M 96·10; n_C 1·46162, n_D 1·46573, n_F 1·47068, $n_{G'}$ 1·48445, R_C 25·78, R_D 25·98, R_F 26·48, $R_{G'}$ 26·87; $Mn_D^{20°}$ 140·85. Densities determined: $d_{4°}^{20°}$ 1·0240, $d_{4°}^{42·9°}$ 0·9958, $d_{4°}^{61·1°}$ 0·9757. Apparatus *C*.

19·2°	11·24	1·0249	27·35	214·4	62·1°	9·58	0·9745	22·16	214·3
42·4	10·39	0·9976	24·61	214·7				Mean	214·4

307. p-*Fluorotoluene.* B. p. 115·5°/756 mm.; M 110·13; n_C 1·46483, n_D 1·46884, n_F 1·47897, $n_{G'}$ 1·48705; R_C 30·51, R_D 30·74, R_F 31·31, $R_{G'}$ 31·76; $Mn_D^{20°}$ 161·76. Densities determined: $d_{4°}^{20°}$ 0·9975, $d_{4°}^{40·7°}$ 0·9784, $d_{4°}^{60·8°}$ 0·9575, $d_{4°}^{85·7°}$ 0·9304. Apparatus *D*.

23·1°	11·37	0·9946	27·93	254·5	61·1°	10·00	0·9572	23·64	253·6
26·9	11·17	0·9911	27·34	254·1	86·0	9·11	0·9301	20·92	253·6
41·1	10·74	0·9780	25·95	254·1				Mean	254·0

308. α-*Fluoronaphthalene.* B. p. 214°/759 mm. and 98°/17 mm.; M 146·16; n_C 1·58604, n_D 1·59388, n_F 1·61464; R_C 43·26, R_D 43·73, R_F 44·96; $Mn_D^{20°}$ 232·96. Densities determined: $d_{4°}^{20°}$ 1·1340, $d_{4°}^{40·0°}$ 1·1168, $d_{4°}^{60·8°}$ 1·0999, $d_{4°}^{86·7°}$ 1·0781. Apparatus *A*.

16·3°	18·35	1·1371	39·07	321·4	60·5°	16·69	1·1001	34·38	321·6
24·9	18·13	1·1299	38·35	321·2	87·4	15·63	1·0775	31·54	321·4
41·2	17·45	1·1166	36·48	321·7				Mean	321·5

309. p-*Chlorotoluene.* B. p. 161·5°/769 mm.; M 126·59; n_C 1·51629, n_D 1·52096, n_F 1·53301, $n_{G'}$ 1·54255; R_C 35·72, R_D 35·99, R_F 36·68, $R_{G'}$ 37·23; $Mn_D^{20°}$ 192·54. Densities determined: $d_{4°}^{20°}$ 1·0710, $d_{4°}^{41·5°}$ 1·0513, $d_{4°}^{61·7°}$ 1·0317, $d_{4°}^{86·7°}$ 1·0077. Apparatus *D*.

18·3°	12·42	1·0726	32·90	282·6	62·1°	11·05	1·0312	28·14	282·7
26·0	12·27	1·0653	32·28	283·2	86·3	10·30	1·0082	25·65	282·6
41·9	11·67	1·0509	30·29	282·6				Mean	282·7

310. m-*Dichlorobenzene.* B. p. 172·5°/760 mm.; M 147·01; n_C 1·54142, n_D 1·54641, n_F 1·55924, $n_{G'}$ 1·56946; R_C 35·89, R_D 36·16, R_F 36·86, $R_{G'}$ 37·42; $Mn_D^{20°}$ 227·34. Densities determined: $d_{4°}^{20°}$ 1·2880, $d_{4°}^{41·0°}$ 1·2654, $d_{4°}^{61·5°}$ 1·2430, $d_{4°}^{86·5°}$ 1·2155. Apparatus *A*.

14·3°	15·08	1·2942	36·54	279·3	61·7°	13·37	1·2428	31·11	279·4
20·0	14·96	1·2880	36·16	279·7	86·4	12·50	1·2156	28·45	279·3
41·8	14·16	1·2645	33·53	279·8				Mean	279·5

311. *Benzenesulphonyl fluoride.* B. p. 208·5°/753 mm.; M 160·16; n_C 1·48816, n_D 1·49229, n_F 1·50285, $n_{G'}$ 1·51135; R_C 34·62, R_D 34·87, R_F 35·50, $R_{G'}$ 36·01; $Mn_D^{20°}$ 239·01. Densities determined: $d_{4°}^{20°}$ 1·3334, $d_{4°}^{39·7°}$ 1·3114, $d_{4°}^{61·4°}$ 1·2879, $d_{4°}^{85·6°}$ 1·2608. Apparatus *A*.

15·0°	15·23	1·3389	38·18	297·4	60·4°	13·73	1·2887	33·13	298·2
17·5	15·18	1·3361	37·98	297·5	85·9	12·96	1·2605	30·59	298·8
39·4	14·47	1·3117	35·54	298·1				Mean	298·0

312. *Benzenesulphonyl chloride.* B. p. 135°/25 mm.; M 176·62; n_C 1·54721, n_D 1·55236, n_F 1·56553, $n_{G'}$ 1·57624; R_C 40·71, R_D 41·03, R_F 40·71, $R_{G'}$ 42·48; $Mn_D^{20°}$ 274·18. Densities determined: $d_4^{20°}$ 1·3762, $d_4^{40·6°}$ 1·3563, $d_4^{62·2°}$ 1·3345, $d_4^{86·7°}$ 1·3092. Apparatus *D*.

t.	H.	$d_{4°}^{t°}$.	γ.	P.	t.	H.	$d_{4°}^{t°}$.	γ.	P.
20·9°	12·72	1·3753	43·20	329·2	60·3°	11·74	1·3364	38·75	329·7
24·9	12·61	1·3713	42·70	329·3	87·4	11·06	1·3085	35·74	330·0
41·1	12·19	1·3558	40·81	329·3				Mean	329·5

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132. *Physical Properties and Chemical Constitution. Part XV. The Phenyl Group.*

By ARTHUR I. VOGEL.

New measurements of the parachors and of the refractivities for the C, D, F, and G′ lines at 20° of a number of alkyl benzoates, phenylacetates, and β-phenylpropionates and of monohalogeno-benzenes are recorded. The experimental data, in conjunction with those in Parts XIII and XIV (preceding papers), have been employed in the calculation of the constants for the phenyl group by the following methods: (1) $C_6H_5{\cdot}CO_2R - 0{\cdot}5(CO_2R)_2$; (2) $C_6H_5{\cdot}CH_2{\cdot}CO_2R - 0{\cdot}5(CH_2{\cdot}CO_2R)_2$; (3) $C_6H_5{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2R - 0{\cdot}5(CH_2{\cdot}CH_2{\cdot}CO_2R)_2$; (4) $C_6H_5X - X$ (X = Cl, Br and I). The results are in reasonable agreement and lead to the following mean values for the phenyl group:

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
C_6H_5	188·3	25·239	25·463	26·036	26·057	121·89

Preliminary figures for the α-naphthyl group have been computed from measurements upon α-methyl-, α-chloro-, and α-bromo-naphthalene.

THE primary object of this investigation was the determination of the parachor and the refractivities for the C, D, F, and G′ lines of the phenyl group. Apart from its own intrinsic value, it is hoped, with the aid of the constants for hydrogen (Part IX, *J.*, 1946, 133) to employ the refractivities in the calculation of the bond refractions $C_{ar.}$–$C_{ar.}$ which will be compared with

TABLE I.

Parachor and refractivities of the phenyl group.

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
From alkyl benzoates, $C_6H_5{\cdot}CO_2R$.						
R = Me	188·6	25·43	25·67	26·32	26·83	123·40
R = Et	187·9	25·53	25·79	26·43	26·96	122·99
R = Pr^n	187·9	25·50	25·74	26·38	26·93	122·98
R = Bu^n	188·2	25·55	25·80	26·44	26·98	122·89
From alkyl phenylacetates, $C_6H_5{\cdot}CH_2{\cdot}CO_2R$.						
R = Me	189·1	25·13	25·34	25·89	26·33	122·56
R = Et	188·8	25·19	25·40	25·95	26·40	122·17
R = Pr^n	189·5	25·18	25·39	25·95	26·38	121·87
R = Bu^n	188·1	25·22	25·44	25·98	26·44	121·69
From alkyl β-phenylpropionates, $C_6H_5{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2R$.						
R = Me	188·6	25·21	25·43	25·98	26·44	122·39
R = Et	187·9	25·16	25·37	25·92	26·39	122·00
R = Pr^n	187·0	25·18	25·40	25·94	26·41	121·89
R = Bu^n	187·1	25·22	25·43	25·99	26·46	121·64
From halogenobenzenes, C_6H_5X.						
X = Cl	188·0	25·08	25·30	25·83	26·25	121·22 *
X = Br	188·3	25·04	25·25	25·79	26·22	126·88 *
X = I	188·9	24·97	25·20	25·75	26·19	134·33 *
Mean	188·3	25·239	25·463	26·036	26·507	121·89 *
Mean (excluding alkyl benzoates)	188·3	25·136	25·359	25·906	26·356	122·03 *

* Values marked with an asterisk were omitted in the calculation of the mean.

the figures deduced from other data (*e.g.*, Part X, this vol., p. 607). New measurements of the parachors and the refractivities have accordingly been made upon the compounds mentioned above. The constants for the phenyl group have been computed by the four methods indicated above. The results are collected in Table I. It will be observed that the results by all methods are in reasonably good agreement, although the refractivities derived from the alkyl benzoates appear to be slightly higher than those from the other series. Whether these differences possess real significance cannot at present be decided, but as a first approximation the constants for the phenyl group have been taken as the arithmetical mean of all the values. It must be pointed out that the experimental data for the dialkyl oxalates lead to constants for CO·O which are higher than the mean figures derived from other carboxylic esters (Part XIII, *loc. cit.*), yet they give reasonable figures for the contribution of the phenyl group. The second set of mean constants for C_6H_5 do not include the data for the alkyl benzoates and are probably more trustworthy.

The experimental results for benzyl chloride (XIV, **281**) (which are not of the same order of accuracy as the other measurements because of the properties of the compound) lead to the following figures for phenyl $\{C_6H_5 = C_6H_5{\cdot}CH_2Cl - (CH_2 + Cl)\}$: P, 189·3, R_C 25·32, R_D 25·53, R_F 26·11, R_G 26·56, $Mn_D^{20°}$ 123·81.

Some preliminary results for the α-naphthyl group, calculated from new experimental measurements upon α-methyl-, α-chloro-, and α-bromo-naphthalene are given in Table II.

TABLE II.

Parachor and refractivities of the α-naphthyl group.

	P.	R_C.	R_D.	R_F.	R_G.	$Mn_D^{20°}$.
$C_{10}H_7{}^{\alpha}{\cdot}CH_3$	293·6	42·50	43·00	44·27	—	210·68
$C_{10}H_7{}^{\alpha}Cl$	293·3	—	42·89	—	—	215·08
$C_{10}H_7{}^{\alpha}Br$	292·6	—	42·66	—	—	225·29

EXPERIMENTAL.

Preparation of Materials.—Methyl benzoate. From A.R. benzoic acid, m. p. 122—123° (1 mol.), absolute methyl alcohol (10 mols.), and concentrated sulphuric acid (5% of weight of the alcohol); b. p. 199°/775 mm.

Ethyl benzoate. From A.R. benzoic acid, absolute ethyl alcohol, and concentrated sulphuric acid, as for the methyl ester; b. p. 213·5°/775 mm.

n-*Propyl benzoate.* From 30·5 g. of A.R. benzoic acid, 30 g. of pure *n*-propyl alcohol, 50 ml. of sodium-dried A.R. benzene, and concentrated sulphuric acid; the mixture was refluxed for 35 hours and then poured into water, etc. The yield was 37 g.; b. p. 229·5°/766 mm.

n-*Butyl benzoate.* From 30·5 g. of A.R. benzoic acid, 37 g. of pure *n*-butyl alcohol, 50 ml. of sodium-dried A.R. benzene, and 10 g. of concentrated sulphuric acid; refluxed for 35 hours. The yield of ester was 36 g., b. p. 120°/11 mm.

Methyl phenylacetate. From phenylacetic acid, m. p. 77—78°, absolute ethyl alcohol, and concentrated sulphuric acid, as for methyl benzoate; b. p. 215°/760 mm.

Ethyl phenylacetate. From phenylacetic acid, absolute ethyl alcohol, and concentrated sulphuric acid; b. p. 228°/753 mm.

n-*Propyl phenylacetate.* From 34 g. of phenylacetic acid, 30 g. of *n*-propyl alcohol, 50 ml. of sodium-dried A.R. benzene, and 10 g. of concentrated sulphuric acid; refluxed for 24 hours. The yield of ester, b. p. 240°/753 mm., was 43 g.

n-*Butyl phenylacetate.* From 34 g. of phenylacetic acid, 37 g. of pure *n*-butyl alcohol, 50 ml. of sodium-dried A.R. benzene, and 10 g. of concentrated sulphuric acid. The yield of ester, b. p. 257°/753 mm., was 45 g.

Methyl β-phenylpropionate. β-Phenylpropionic acid was prepared by reduction of purified ethyl cinnamate in moist ethereal solution with aluminium amalgam (Vogel, *J.*, 1927, 597); the resulting ethyl ester, b. p. 248—250°/760 mm., was hydrolysed with alcoholic potassium hydroxide solution and, after recrystallisation from water or from dilute methyl alcohol, the acid had m. p. 49—50°. The methyl ester was prepared from this acid, excess of absolute methyl alcohol, and concentrated sulphuric acid; b. p. 231·5—232·5°/755 mm.

Ethyl β-phenylpropionate. From 25 g. of the acid, 23 g. of absolute ethyl alcohol, 100 ml. of dry benzene, and 4 g. of concentrated sulphuric acid; refluxed for 16·5 hours. The yield of ester, b. p. 123°/11 mm., was 26 g.

n-*Propyl β-phenylpropionate.* From 25 g. of the acid, 30 g. of *n*-propyl alcohol, 100 ml. of dry benzene, and 4 g. of concentrated sulphuric acid; refluxed for 16·5 hours. The yield of ester, b. p. 126°/9 mm., was 27 g.

n-*Butyl β-phenylpropionate.* From 25 g. of the acid, 37 g. of *n*-butyl alcohol, 100 ml. of dry benzene, and 4 g. of concentrated sulphuric acid; refluxed for 18 hours. The yield of *n-butyl* ester, b. p. 138°/6 mm., was 34 g. (Found: C, 75·9; H, 9·0. $C_{13}H_{18}O_2$ requires C, 75·7; H, 8·8%).

Chlorobenzene. This was prepared from A.R. aniline by an adaptation of the method given for *o*-chlorotoluene (*Org. Synth.*, 1923, **3**, 35); the crude product was washed with sodium hydroxide solution, cold concentrated sulphuric acid (to remove traces of azo-compounds), and then water until neutral, dried, and distilled; b. p. 131·5°/765 mm.

Bromobenzene. This was prepared from A.R. aniline (see details for *p*-bromotoluene in *Org. Synth.*, 1925, **5**, 21) and purified as for chlorobenzene; treatment with one-third of the volume of concentrated sulphuric acid produced a very dark solution and the product was therefore poured into excess of water to separate the bromobenzene. The latter was washed with dilute sodium hydroxide solution and water, dried, and distilled: the product boiled constantly at 155°/755 mm. and was extremely pale yellow in colour.

A second sample was prepared by washing a pure commercial product (obviously prepared directly from benzene) with sodium hydrogen carbonate solution and water, dried, and distilled: this boiled at 155°/760 mm., was perfectly colourless, and had identical physical properties with the preparation from aniline.

Iodobenzene. This was prepared from A.R. aniline (*Org. Synth.*, 1939, **19**, 55) and boiled at 186°/750 mm. as a yellow liquid. Redistillation gave a colourless product, b. p. 58°/6 mm.

α-Methylnaphthalene. A pure commercial product was washed three times with one-third of its bulk of 10% sodium hydroxide solution, then with water until the washings were neutral, and dried ($MgSO_4$) and twice distilled over sodium; b. p. 240·5°/760 mm.

α-Chloronaphthalene. A pure commercial product was washed successively with 10% sodium hydroxide solution and water, dried, and twice fractionated under reduced pressure; b. p. 106·5°/5 mm.

α-Bromonaphthalene. A pure commercial product was purified as for α-chloronaphthalene; b. p. 125·5°/5 mm.

Physical Measurements.—All liquids were redistilled immediately before use; the b. p.s are given below.

313. *Methyl benzoate.* B. p. 199°/775 mm.; M 136·14; n_C 1·51213, n_D 1·51701, n_F 1·52970, $n_{G'}$ 1·53992; R_C 37·51, R_D 37·81, R_F 38·59, $R_{G'}$ 39·20; $Mn_D^{20°}$ 205·86. Densities determined: $d_{4°}^{20°}$ 1·0894, $d_{4°}^{41·1°}$ 1·0690, $d_{4°}^{60·7°}$ 1·0505, $d_{4°}^{85·5°}$ 1·0280. Apparatus *A*.

(These headings apply to corresponding columns in all the following tables.)

t.	H.	$d_{4°}^{t°}$.	γ.	P.	t.	H.	$d_{4°}^{t°}$.	γ.	P.
15·3°	18·69	1·0949	38·32	309·4	61·8°	16·65	1·0494	32·72	310·3
20·3	18·54	1·0891	37·81	309·9	87·3	15·60	1·0263	29·98	310·4
41·1	17·60	1·0690	35·23	310·3				Mean	310·1

314. *Ethyl benzoate.* B. p. 213·5°/775 mm.; M 150·17; n_C 1·50064, n_D 1·50519, n_F 1·51689, $n_{G'}$ 1·52654; R_C 42·24, R_D 42·57, R_F 43·40, $R_{G'}$ 44·07; $Mn_D^{20°}$ 226·04. Densities determined: $d_{4°}^{20°}$ 1·0467, $d_{4°}^{41·5°}$ 1·0276, $d_{4°}^{61·6°}$ 1·0099, $d_{4°}^{86·3°}$ 0·9876. Apparatus *D*.

15·8°	13·67	1·0504	35·46	348·9	41·9°	12·88	1·0272	32·67	349·5
21·1	13·56	1·0457	35·02	349·3	62·1	12·21	1·0095	30·44	349·4
24·8	13·43	1·0424	34·57	349·3	88·1	11·47	0·9860	27·93	350·1
								Mean	349·4

315. n-*Propyl benzoate.* B. p. 229·5°/766 mm.; M 164·20; n_C 1·49598, n_D 1·50031, n_F 1·51134, $n_{G'}$ 1·52043; R_C 46·88, R_D 47·22, R_F 48·10, $R_{G'}$ 48·82; $Mn_D^{20°}$ 246·35. Densities determined: $d_{4°}^{20°}$ 1·0232, $d_{4°}^{41·1°}$ 1·0049, $d_{4°}^{60·4°}$ 0·9878, $d_{4°}^{87·5°}$ 0·9647. Apparatus *A*.

16·0°	18·12	1·0267	35·09	389·2	61·6°	16·15	0·9868	29·84	388·9
23·5	17·73	1·0202	33·87	388·3	87·6	15·12	0·9646	27·31	389·1
41·5	17·03	1·0046	32·04	388·9				Mean	388·9

316. n-*Butyl benzoate.* B. p. 120°/11 mm.; M 178·22; n_C 1·49306, n_D 1·49720, n_F 1·50780, $n_{G'}$ 151631; R_C 51·53, R_D 51·90, R_F 52·83, $R_{G'}$ 53·58; $Mn_D^{20°}$ 266·83. Densities determined: $d_{4°}^{20°}$ 1·0052, $d_{4°}^{41·5°}$ 0·9880, $d_{4°}^{60·1°}$ 0·9725, $d_{4°}^{86·7°}$ 0·9502. Apparatus *A*.

20·8°	17·83	1·0045	33·54	427·0	61·4°	16·31	0·9714	29·67	428·2
26·9	17·71	0·9995	33·15	427·8	87·2	15·30	0·9496	27·21	428·6
41·9	17·01	0·9875	31·45	427·4				Mean	427·8

317. *Methyl phenylacetate.* B. p. 215°/760 mm.; M 150·17; n_C 1·50277, n_D 1·50686, n_F 1·51715 $n_{G'}$ 1·52553; R_C 41·55, R_D 41·84, R_F 42·56, $R_{G'}$ 43·13; $Mn_D^{20°}$ 226·29. Densities determined: $d_{4°}^{20°}$ 1·0679, $d_{4°}^{41·3°}$ 1·0479, $d_{4°}^{60·5°}$ 1·0303, $d_{4°}^{86·7°}$ 1·0065. Apparatus *D*.

18·1°	14·55	1·0697	38·44	349·4	61·5°	13·10	1·0294	33·30	350·4
41·4	13·70	1·0478	35·45	349·7	85·8	12·26	1·0073	30·49	350·3
								Mean	350·0

318. *Ethyl phenylacetate.* B. p. 228°/753 mm.; M 164·18; n_C 1·49347, n_D 1·49734, n_F 1·50705, $n_{G'}$ 1·51492; R_C 46·25, R_D 46·55, R_F 47·33, $R_{G'}$ 47·94; $Mn_D^{20°}$ 245·83. Densities determined: $d_{4°}^{20°}$ 1·0325, $d_{4°}^{42·0°}$ 1·0131, $d_{4°}^{61·5°}$ 0·9948, $d_{4°}^{85·0°}$ 0·9743. Apparatus *D*.

16·7°	13·97	1·0355	35·74	387·6	61·0°	12·50	0·9953	30·72	388·4
20·0	13·86	1·0325	35·34	387·7	84·7	11·77	0·9746	28·33	388·6
41·2	13·22	1·0138	33·10	388·4				Mean	388·1

319. n-*Propyl phenylacetate.* B. p. 240°/753 mm.; M 178·22; n_C 1·48882, n_D 1·49250, n_F 1·50187 $n_{G'}$ 1·50924; R_C 50·89, R_D 51·22, R_F 52·05, $R_{G'}$ 52·69; $Mn_D^{20°}$ 265·99. Densities determined: $d_{4°}^{20}$ 1·0103, $d_{4°}^{41·5°}$ 0·9920, $d_{4°}^{62·0°}$ 0·9743, $d_{4°}^{85·2°}$ 0·9540. Apparatus *A*.

t.	*H.*	$d^{t°}_{4°}$.	*γ.*	*P.*	*t.*	*H.*	$d^{t°}_{4°}$.	*γ.*	*P.*
15·7°	18·33	1·0140	34·80	426·9	60·9°	16·46	0·9752	30·06	427·9
20·9	18·10	1·0095	34·21	427·0	86·3	15·50	0·9532	27·67	428·8
41·2	17·26	0·9923	32·07	427·4				Mean	427·6

320. n-*Butyl phenylacetate.* B. p. 257°/753 mm.; *M* 192·25; n_C 1·48581, n_D 1·48940, n_F 1·49842, $n_{G'}$ 1·50562; R_C 55·54, R_D 55·89, R_F 56·76, $R_{G'}$ 57·45; $Mn_D^{20°}$ 286·34. Densities determined: $d^{20°}_{4°}$ 0·9935, $d^{42·1°}_{4°}$ 0·9755, $d^{39·1°}_{4°}$ 0·9614, $d^{36·1°}_{4°}$ 0·9389. Apparatus *D*.

22·3°	13·52	0·9916	33·11	465·1	62·0°	12·33	0·9590	29·20	466·0
43·1	12·91	0·9747	31·08	465·7	85·2	11·63	0·9396	26·99	466·3
								Mean	465·8

321. *Methyl β-phenylpropionate.* B. p. 232°/755 mm.; *M* 164·20; n_C 1·49903, n_D 1·50297, n_F 1·51297, $n_{G'}$ 1·52089; R_C 46·22, R_D 46·53, $R_{F'}$ 47·31, $R_{G'}$ 47·92; $Mn_D^{20°}$ 246·79. Densities determined: $d^{20°}_{4°}$ 1·0432, $d^{41·0°}_{4°}$ 1·0254, $d^{40·6°}_{4°}$ 1·0077, $d^{37·3°}_{4°}$ 0·9841. Apparatus *D*.

13·9°	14·72	1·0485	38·12	389·1	41·2°	13·86	1·0252	35·09	389·8
16·2	14·64	1·0465	37·84	389·2	61·3	13·16	1·0071	32·73	390·0
22·6	14·44	1·0409	37·12	389·4	87·1	12·33	0·9843	29·97	390·3
								Mean	389·6

322. *Ethyl β-phenylpropionate.* B. p. 123°/11 mm.; *M* 178·22; n_C 1·49086, n_D 1·49460, n_F 1·50401, $n_{G'}$ 1·51158; R_C 50·82, R_D 51·14, R_F 51·97, $R_{G'}$ 52·63; $Mn_D^{20°}$ 266·37. Densities determined: $d^{20°}_{4°}$ 1·0155, $d^{41·0°}_{4°}$ 0·9980, $d^{39·6°}_{4°}$ 0·9815, $d^{35·2°}_{4°}$ 0·9616. Apparatus *D*.

25·5°	13·80	1·0109	34·45	427·1	62·3°	12·65	0·9792	30·59	428·0
28·8	13·73	1·0081	34·18	427·5	86·7	11·88	0·9603	28·17	427·6
40·9	13·31	0·9981	32·81	427·3				Mean	427·5

323. n-*Propyl β-phenylpropionate.* B. p. 126°/9 mm.; *M* 192·17; n_C 1·48769, n_D 1·49131, n_F 1·50041, $n_{G'}$ 1·50774; R_C 55·46, R_D 55·81, R_F 56·68, $R_{G'}$ 57·38; $Mn_D^{20°}$ 286·73. Densities determined: $d^{20°}_{4°}$ 0·9983, $d^{42·5°}_{4°}$ 0·9797, $d^{41·4°}_{4°}$ 0·9638, $d^{36·8°}_{4°}$ 0·9424. Apparatus *A*.

25·0°	18·06	0·9941	33·62	465·7	62·7°	16·48	0·9627	29·71	466·3
32·3	17·84	0·9880	33·00	466·4	87·4	15·43	0·9417	27·21	466·3
42·0	17·33	0·9801	31·80	465·9				Mean	466·1

324. n-*Butyl β-phenylpropionate.* B. p. 138°/6 mm.; *M* 206·27; n_C 1·48512, n_D 1·48864, n_F 1·49743, $n_{G'}$ 1·50441; R_C 60·11, R_D 60·48, R_F 61·41, $R_{G'}$ 62·14; $Mn_D^{20°}$ 307·05. Densities determined: $d^{20°}_{4°}$ 0·9836, $d^{40·4°}_{4°}$ 0·9676, $d^{41·6°}_{4°}$ 0·9506, $d^{36·6°}_{4°}$ 0·9304. Apparatus *D*.

19·3°	13·79	0·9842	33·52	504·3	43·5°	13·12	0·9651	31·27	505·4
22·0	13·74	0·9820	33·32	504·7	62·6	12·56	0·9497	29·46	506·0
29·4	13·56	0·9762	32·69	505·2	87·4	11·86	0·9298	27·23	506·8
								Mean	505·4

325. *Chlorobenzene.* B. p. 131·5°/765 mm.; *M* 112·56; n_C 1·51998, n_D 1·52481, n_F 1·53716, $n_{G'}$ 1·54672; R_C 30·90, R_D 31·14, R_F 31·75, $R_{G'}$ 32·22; $Mn_D^{20°}$ 171·63. Densities determined: $d^{20°}_{4°}$ 1·1074, $d^{41·3°}_{4°}$ 1·0845, $d^{61·0°}_{4°}$ 1·0640, $d^{80·6°}_{4°}$ 1·0432. Apparatus *B*.

16·7°	12·71	1·1109	33·11	243·1	63·4°	11·18	1·0625	28·11	243·4
42·4	11·83	1·0833	30·05	243·3	87·6	10·33	1·0358	25·09	243·2
								Mean	243·2

326. *Bromobenzene.* B. p. 155°/755 mm.; *M* 157·02; n_C 1·55455, n_D 1·55998, n_F 1·57387, n_G 1·58498; R_C 33·72, R_D 33·99, R_F 34·68, $R_{G'}$ 35·23; $Mn_D^{20°}$ 244·95. Densities determined: $d^{20°}_{4°}$ 1·4939, $d^{40·9°}_{4°}$ 1·4676, $d^{60·1°}_{4°}$ 1·4424, $d^{85·2°}_{4°}$ 1·4093. Apparatus *B*.

19·0°	10·26	1·4952	35·97	257·2	62·5°	9·13	1·4393	30·81	257·0
41·2	9·70	1·4672	33·37	257·2	86·5	8·53	1·4076	28·16	257·0
								Mean	257·1

327. *Iodobenzene.* B. p. 186°/750 mm. and 58°/6 mm.; *M* 204·02; n_C 1·61342, n_D 1·62040, n_F 1·63842, $n_{G'}$ 1·65350; R_C 38·80, R_D 39·15, R_F 40·06, $R_{G'}$ 40·81; $Mn_D^{20°}$ 330·60. Densities determined: $d^{20°}_{4°}$ 1·8313, $d^{41·1°}_{4°}$ 1·8016, $d^{60·9°}_{4°}$ 1·7725, $d^{87·7°}_{4°}$ 1·7331. Apparatus *A* and apparatus *B*.*

18·4°	11·47	1·8336	39·38	278·7	41·6° *	8·78	1·8009	37·08	279·5
41·3	10·96	1·8013	36·97	279·3	64·4 *	8·21	1·7675	34·03	278·8
62·2	10·49	1·7706	34·78	279·8	90·0 *	7·74	1·7295	31·39	279·2
								Mean	279·2

[Sugden (*J.*, 1924, **125**, 1172 and 1182) finds *P* for bromobenzene and iodobenzene 260·6 and 282·3, respectively; these values are about 3 units high.]

328. *α-Methylnaphthalene.* B. p. 240·5°/763 mm.; *M* 142·19; n_C 1·60137, n_D 1·60923, n_F 1·63030; R_C 48·14, R_D 48·65, R_F 49·99; $Mn_D^{20°}$ 228·81. Densities determined: $d_{4°}^{20°}$ 1·0123, $d_{4°}^{41·0°}$ 0·9979, $d_{4°}^{59·7°}$ 0·9847, $d_{4°}^{85·4°}$ 0·9660. Apparatus *A*.

t.	*H.*	$d_{4°}^{t°}$.	*γ.*	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	*γ.*	*P.*
18·3°	20·16	1·0135	38·26	348·9	61·6°	18·57	0·9834	34·20	349·8
25·8	19·87	1·0082	37·51	349·2	87·2	17·61	0·9647	31·81	350·0
40·9	19·37	0·9980	36·20	349·7				Mean	349·5

329. *α-Chloronaphthalene.* B. p. 106·5°/5 mm.; *M* 162·62; n_D 1·63255; R_D 48·75; $Mn_D^{20°}$ 265·49. Densities determined: $d_{4°}^{20°}$ 1·1908, $d_{4°}^{41·4°}$ 1·1741, $d_{4°}^{62·8°}$ 1·1572, $d_{4°}^{86·0°}$ 1·1394. Apparatus *D*.

15·9°	14·59	1·1941	43·03	348·8	61·0°	13·27	1·1586	37·97	348·4
25·5	14·18	1·1864	41·55	348·0	86·4	12·60	1·1383	35·42	348·5
40·5	13·87	1·1748	40·24	348·6				Mean	348·5

330. *α-Bromonaphthalene.* B. p. 125·5°/5 mm.; *M* 207·08; n_D 1·65805, R_D 51·40; $Mn_D^{20°}$ 343·36. Densities determined: $d_{4°}^{20°}$ 1·4839, $d_{4°}^{40·8°}$ 1·4659, $d_{4°}^{60·2°}$ 1·4470, $d_{4°}^{86·0°}$ 1·4225. Apparatus *D*.

16·2°	12·32	1·4874	45·26	361·1	60·4°	11·44	1·4468	40·88	361·9
27·0	12·11	1·4775	44·19	361·4	86·7	10·79	1·4219	37·89	361·3
41·0	11·89	1·4654	43·03	361·9				Mean	361·5

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133. *Physical Properties and Chemical Constitution. Part XVI. Ethylenic Compounds.*

By GEORGE H. JEFFERY and ARTHUR I. VOGEL.

New measurements are presented of the parachors and the refractivities (20°) for esters of vinylacetic, undecylenic, and allylmalonic acid, for unsaturated aliphatic hydrocarbons, and for allyl esters of aliphatic monobasic acids and of succinic acid. The contributions of the carbon–carbon double bond have been computed from the general relationship $\digamma = CR_1R_2{:}CR_3R_4 + 2H - CHR_1R_2{\cdot}CHR_3R_4$, employing the values for 2H from Part IX (*J.*, 1946, 133) and the appropriate saturated compounds to be found in previous papers of this series. These lead to the following mean values:

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
$\digamma$	19·9	1·545	1·575	1·672	1·720	−6·07

These constants differ considerably from those previously accepted.

Similar measurements have also been made upon alkyl maleates and fumarates, citraconates and mesaconates, methylsuccinates, *trans*-crotonates, and cinnamates. The ethylenic double-bond contributions were similarly calculated and possessed the following values:

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
Maleates	19·6	2·24	2·31	2·47	2·60	−4·54
Fumarates	22·3	2·86	2·96	3·24	3·44	−4·19
Citraconates	21·8	2·42	2·50	2·72	2·88	−3·41
Mesaconates	18·6	2·71	2·81	3·09	3·33	−2·50
trans-Crotonates	21·3	2·23	2·30	2·49	2·62	−4·32
Cinnamates	21·0	4·96	5·26	6·14	7·06	−3·29

THE parachor increment for the carbon–carbon double bond, given as 23·2 by Sugden (see Sugden, *J.*, 1924, **125**, 1177; Sugden, Reed, and Wilkins, *J.*, 1925, **127**, 1525), was apparently based upon data for ethylene, propylene, amylene, and diallyl. Eisenlohr (*Z. physikal. Chem.*, 1910, **75**, 604) has utilised the figures for " amylene, hexylene, octylene, decylene, allyl alcohol, allyl acetate, allyl ethyl ether, allyl acetone, butenyl dimethyl carbinol, allyl methyl propyl carbinol, tetrahydrobenzene, valerylene, diallyl, *d*-limonene, sylvestrene, diallyl acetone and diallyl acetic acid " for the evaluation of the refractivities of the double bond and gives the following mean values:

	R_C.	R_D.	R_F.	$R_{G'}$.
$\digamma$	1·686	1·733	1·824	1·893

It is clear that the resulting constants are not altogether satisfactory since, apart from the not too happy choice of compounds for the deduction of such fundamental constants, the CH_2

values themselves employed in the computations are subject to error (compare Part IX, *J.*, 1946, 133). The authors have employed five independent series of compounds in their own determinations of the constants of the C=C double bond, *viz.*: (1) Esters of vinylacetic acid; (2) esters of undecylenic acid; (3) unsaturated aliphatic hydrocarbons; (4) esters of allylmalonic acid; (5) allyl esters of monobasic acids and also of succinic acid. The general method of calculation of the constants may be expressed by:

$$\overline{=} = CR_1R_2{:}CR_3R_4 + 2H - CHR_1R_2{\cdot}CHR_3R_4$$

It will be noted that the procedure does not involve a knowledge of the values of the CH_2 increment. The values for H are those of Part IX (*loc. cit.*), the saturated hydrocarbons are from Part IX (*loc. cit.*), and the saturated esters are given in Part XIII (this vol., p. 624). No experimental data are available for esters of *n*-undecylic acid $CH_3{\cdot}[CH_2]_9{\cdot}CO_2R$ required in the calculations under (2), but the necessary figures have been evaluated with sufficient accuracy by taking the mean values deduced from (*a*) the experimental data for *n*-decoates and *n*-dodecoates, *i.e.*, $0{\cdot}5\{CH_3{\cdot}[CH_2]_8{\cdot}CO_2R + CH_3{\cdot}[CH_2]_{10}{\cdot}CO_2R\}$ (Part XIII, *loc. cit.*) and (*b*) the experimental data for *n*-decoates (Part XIII, *loc. cit.*) and CH_2 (Part IX, *loc. cit.*), *i.e.*, from $CH_3{\cdot}[CH_2]_8{\cdot}CO_2R + CH_2$. The figures obtained by methods (*a*) and (*b*) were in excellent agreement.

All the compounds, with the exception of octene to hexadecene, were prepared by the authors from the purest available starting materials. The unsaturated hydrocarbons (octene to hexadecene) were commercial products and were carefully purified: nevertheless, the final purity cannot confidently be stated to be as high as those of the other unsaturated compounds because data for the purity of the normal alcohols from which they were prepared are not available. The physical properties are, however, in good agreement with those recently

TABLE I.

Values for carbon–carbon double bond from ethylenic compounds (20°).

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
Esters of vinylacetic acid, $CH_2{:}CH{\cdot}CH_2{\cdot}CO_2R$.						
R = H	19·6	1·54	1·57	1·66	1·71	−5·68
R = Me	20·4	1·54	1·57	1·66	1·69	−5·84
R = Et	19·7	1·49	1·53	1·62	1·66	−5·78
R = Pr^n	19·7	1·53	1·57	1·65	1·70	−5·95
R = Bu^n	19·5	1·54	1·59	1·69	1·72	−5·98
R = Am^n	19·0	1·52	1·56	1·65	1·68	−5·95
Esters of undecylenic acid, $CH_2{:}CH{\cdot}[CH_2]_8{\cdot}CO_2R$.						
R = Me	21·0	1·62	1·64	1·75	1·78	−6·02
R = Et	20·5	1·55	1·56	1·65	1·70	−5·95
R = Pr^n	20·6	1·56	1·60	1·70	1·74	−5·92
R = Bu^n	19·7	1·57	1·59	1·68	1·74	−5·72
Unsaturated aliphatic hydrocarbons.						
C_5H_{10}	18·3	1·59	1·61	1·72	1·79	−6·48
C_6H_{12}	21·1	1·54	1·57	1·68	1·73	−6·48
C_8H_{16}	19·7	1·60	1·65	1·74	1·80	−6·63
$C_{10}H_{20}$	20·2	1·51	1·52	1·63	1·71	−6·72
$C_{12}H_{24}$	20·2	1·55	1·57	1·69	1·74	−6·59
$C_{14}H_{28}$	19·4	1·49	1·51	1·62	1·68	−6·51
$C_{16}H_{30}$	20·4	1·56	1·58	1·71	1·74	−6·52
Diallyl	20·3	1·58	1·61	1·71	1·76	−6·76
Esters of allylmalonic acid, $C_3H_5{\cdot}CH(CO_2R)_2$.						
R = Me	19·7	1·55	1·59	1·68	1·72	−5·64
R = Et	19·1	1·50	1·52	1·61	1·66	−5·81
R = Pr^n	19·9	1·50	1·53	1·63	1·67	−5·92
R = Bu^n	19·5	1·56	1·59	1·67	1·74	−5·96
Allyl esters of aliphatic acids.						
$CH_3{\cdot}CO_2C_3H_5$	20·6	1·46	1·50	1·59	1·62	−5·96
$CH_3{\cdot}CH_2{\cdot}CO_2C_3H_5$	20·4	1·56	1·59	1·69	1·73	−5·95
$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2C_3H_5$	19·0	1·53	1·57	1·66	1·72	−5·85
$(CH_2{\cdot}CO_2C_3H_5)_2$	20·7	1·62	1·65	1·74	1·78	−5·36
Mean	19·9	1·545	1·575	1·672	1·720	−6·07

published for alkenes with terminal double bond by Wibaut and Geldof (*Rec. Trav. chim.*, 1946, **65**, 125), but here also no evidence of purity has, so far, been given. There seems, however, to be no adequate reason for excluding the results for the alkenes from the calculation of the mean values for the ethylenic linkage.

The results are collected in Table I. It will be observed that the mean values differ considerably from the previously accepted figures.

The values for the ethylenic bond deduced from allyl halides, 2H, and the propyl halides (Part VIII, *J.*, 1943, 636) are shown below. The unsatisfactory result for allyl bromide may be connected with its relative instability.

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
$CH_2{:}CH{\cdot}CH_2Cl$	19·3	1·59	1·63	1·73	1·79	−5·81
$CH_2{:}CH{\cdot}CH_2Br$	20·2	1·89	1·94	2·08	2·15	−3·81

We have also measured the parachors and refractivities of a series of dialkyl maleates and fumarates and also of dialkyl citraconates and mesaconates. The double-bond contributions for the former pair were calculated with the aid of the experimental figures for dialkyl succinates (Part XIII, *loc. cit.*), and for the latter new experimental data for dialkyl methylsuccinates have been provided. The results are collected in Table II. It will be observed that whilst the parachor contributions appear to be fairly constant, the *cis*-isomers seem to give lower values for the refractivities than the corresponding *trans*-isomers. The absolute values are different in the two pairs of *cis-trans*-isomerides, and all the values are higher than those for the simple ethylenic compounds because of conjugation.

TABLE II.

Values for carbon–carbon double bond for cis-trans-*esters* (20°).

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
Dialkyl maleates, $CO_2R{\cdot}CH{:}CH{\cdot}CO_2R$.						
R = Me	21·6	2·20	2·25	2·41	2·54	−4·69
R = Et	19·6	2·26	2·34	2·51	2·62	−4·47
R = Pr^n	20·7	2·19	2·27	2·43	2·53	−4·35
R = Bu^n	18·7	2·28	2·35	2·52	2·65	−4·46
R = Bu^i	19·8	2·40	2·46	2·68	2·82	−4·56
R = Am^n	19·0	2·22	2·30	2·48	2·57	−4·61
R = Am^i	—	2·14	2·20	2·38	2·47	−4·63
Mean	19·6	2·24	2·31	2·47	2·60	−4·54
Dialkyl fumarates, $CO_2R{\cdot}CH{:}CH{\cdot}CO_2R$.						
R = Et	22·2	2·85	2·96	3·22	3·40	−4·36
R = Pr^n	22·7	2·82	2·92	3·19	3·37	−4·23
R = Bu^n	21·9	2·86	2·96	3·22	3·46	−4·12
R = Bu^i	24·2	2·91	3·00	3·28	3·51	−4·24
R = Am^n	21·9	2·92	3·02	3·31	3·52	−4·09
R = Am^i	21·1	2·82	2·91	3·20	3·39	−4·12
Mean	22·3	2·86	2·96	3·24	3·44	−4·19
Dialkyl citraconates, $CO_2R{\cdot}CH{:}CMe{\cdot}CO_2R$.						
R = Me	22·9	2·39	2·46	2·70	2·82	−3·53
R = Et	21·4	2·43	2·51	2·72	2·91	−3·28
R = Pr^n	20·4	2·44	2·52	2·74	2·91	−3·41
Mean	21·8	2·42	2·50	2·72	2·88	−3·41
Dialkyl mesaconates, $CO_2R{\cdot}CH{:}CMe{\cdot}CO_2R$.						
R = Me	17·9	2·62	2·71	2·99	3·21	−2·44
R = Et	18·9	2·68	2·79	3·07	3·33	−2·53
R = Pr^n	19·1	2·82	2·92	3·21	3·45	−2·53
Mean	18·6	2·71	2·81	3·09	3·33	−2·50

The results of similar measurements and computations for alkyl crotonates and alkyl cinnamates are summarised in Tables III and IV, respectively. The experimental data for alkyl *n*-butyrates required as reference compounds for the former are in Part XIII (*loc. cit.*) and those for alkyl β-phenylpropionates are in Part XV (preceding paper).

TABLE III.

Values for carbon–carbon double bond from alkyl trans-*crotonates*, $CH_3 \cdot CH{:}CH \cdot CO_2R$.

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
R = Me	21·6	2·25	2·32	2·51	2·63	−4·08
R = Et	21·4	2·27	2·34	2·53	2·66	−4·22
R = Pr^n	21·3	2·19	2·26	2·45	2·59	−4·23
R = Bu^n	21·4	2·25	2·32	2·51	2·64	−4·24
R = Am^n	21·1	2·21	2·27	2·47	2·60	−4·26
R = Am^i	21·1	2·20	2·29	2·46	2·61	−4·33
Mean	21·3	2·23	2·30	2·49	2·62	−4·32

TABLE IV.

Values for carbon–carbon double bond from alkyl cinnamates, $C_6H_5 \cdot CH{:}CH \cdot CO_2R$.

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
R = Et	21·3	4·90	5·20	6·07	—	−3·36
R = Pr^n	21·3	5·00	5·30	6·20	7·06	−3·27
R = Bu^n	20·4	4·97	5·27	6·17	7·06	−3·25
Mean	21·0	4·96	5·26	6·14	7·06	−3·29

EXPERIMENTAL.

Esters of Vinylacetic Acid.—Allyl cyanide. The following modification of the procedure of *Org. Synth.*, Coll. Vol. I, 1941, 46, gave an improved yield. In a 1·5-l. three-necked flask, equipped with two efficient double-surface condensers, was placed a mixture of 226 g. of dry cuprous cyanide (Barber, *J.*, 1943, 79) and 293 g. of freshly distilled allyl bromide, b. p. 70—71°/751 mm. The mixture was gently refluxed on a water-bath; after 15 minutes a very vigorous reaction set in, and the water-bath was immediately replaced by an ice-water-bath. When the reaction had subsided, a mercury-sealed mechanical stirrer was introduced into the central aperture of the flask and the mixture was heated, with stirring, on a water-bath for 1 hour. The allyl cyanide, isolated as detailed in *Org. Synth.*, boiled at 116—121°/754 mm. and weighed 145 g.

Vinylacetic acid. This was prepared from allyl cyanide as in *Org. Synth.*, 1944, **24**, 96: distillation of the dried (Na_2SO_4) ethereal extract of the acid always gave a small low-b. p. fraction from which water separated on standing; the pure acid was readily obtained from this by separating the water, drying ($CaSO_4$) and distilling. The yield of vinylacetic acid, b. p. 73—74°/14 mm. (mainly 72·5°/14 mm.), from 140 g. of the nitrile was 120 g. Upon redistillation, the acid boiled constantly at 77·5°/19 mm. and a middle fraction was removed for the physical measurements.

The pure acid can readily be obtained by distillation under diminished pressure and, contrary to *Org. Synth.* (*loc. cit.*), no by-products which cannot be removed by distillation were found. The purification procedure described in *Org. Synth.* leads to considerable loss and it is doubtful whether the purity of the acid is improved. Linstead, Noble, and Boorman (*J.*, 1933, 560) give for the pure acid, b. p. 69°/10 mm., 78°/21 mm., $d_4^{20°}$ 1·0090—1·0098, $n_D^{20°}$ 1·4220—1·4222.

Vinylacetyl chloride. 150 G. of pure thionyl chloride (redistilled over quinoline; b. p. 77°/768 mm.). were placed in a 500-ml. round-bottomed flask fitted (ground glass joint) with a double-surface condenser, and 95 g. of pure vinylacetic acid were slowly added during 1 hour. The mixture was refluxed for 30 minutes, the reflux condenser replaced by an all-glass Dufton column, etc., and the mixture fractionated: 87 g. of vinylacetyl chloride, b. p. 98—99°/774 mm., were obtained.

Methyl vinylacetate. 8·1 G. of pure anhydrous methyl alcohol contained in an all-glass apparatus (250 ml. flask, reflux condenser and dropping-funnel, both protected by calcium chloride drying tubes) were cooled to 0° and 24 g. of vinylacetyl chloride were added during 30 minutes. The mixture was kept at room temperature for 1 hour, poured into excess of water, the ester separated, washed successively with saturated sodium hydrogen carbonate solution and water, and then dried ($CaSO_4$). Distillation from a Claisen flask with fractionating side arm gave 15 g. of the pure *methyl* ester, b. p. 108—108·5°/774 mm. (Found: C, 59·8; H, 8·2. $C_5H_8O_2$ requires C, 60·0; H, 8·1%).

Ethyl vinylacetate. Method 1. The interaction of 11·2 g. of absolute ethyl alcohol and 26 g. of vinylacetyl chloride exactly as for the methyl ester gave, after standing for 1 hour at the laboratory temperature and working up as usual, 17·5 g. of ester, b. p. 124·5—126·5°/760 mm., and 2 g. of b. p. 126·5—140°: there was no appreciable residue in the flask. Redistillation of the main fraction afforded the pure ester, b. p. 124°/745 mm.

In another experiment with 8·4 g. of absolute ethyl alcohol and 18 g. of vinylacetyl chloride, the reaction mixture was kept overnight and then worked up as usual. Fractionation then yielded (*a*) b. p. 125—127°/774 mm., 7 g. [ethyl vinylacetate, $d_4^{20°}$ 0·9177, $n_D^{20°}$ 1·4110, R_D 30·88, P (mean) 281·9]; (*b*) b. p. 127—140°/774 mm., 2 g. (probably largely ethyl crotonate); and (*c*) b. p. 140—170°/774 mm., mainly 168—170°, 2 g. (ethyl β-chlorobutyrate). It is evident that prolonged contact of the reaction product with the hydrogen chloride produced in the reaction should be avoided when the pure alkyl vinylacetate is required.

Method 2. Silver vinylacetate was prepared by cooling a mixture of 95 g. of vinylacetic acid and 200 ml. of water in ice and adding dropwise and with mechanical stirring the theoretical quantity of ammonia solution (342 ml. of 3·2N); a solution of 206 g. of silver nitrate in 500 ml. of water was then added with stirring. About 1500 ml. of water were run into the thick suspension, and the solid was filtered off, washed with water and then rectified spirit, and dried at 40°. The yield of silver salt was 112 g.; it was finely ground and kept in a vacuum desiccator covered with brown paper.

A mixture of 38 g. of dry silver vinylacetate, 31 g. of ethyl iodide, and 50 ml. of sodium-dried A.R. benzene was refluxed for 30 hours, and the precipitate filtered off and washed with dry benzene. The combined filtrate and extracts was washed successively with sodium hydrogen carbonate solution and water, dried ($CaSO_4$), and distilled. The resulting ester (7 g.) boiled at 122—128° and was unsatisfactory for the physical measurements. Boorman, Linstead, and Rydon (*J.*, 1933, 573) give for the ester prepared from the silver salt and ethyl iodide $d_4^{20°}$ 0·9192, $n_D^{20°}$ 1·4102 but do not record a b. p.

n-*Propyl vinylacetate*. *Method* 1. The interaction between 13·2 g. of pure, dry *n*-propyl alcohol and 21 g. of vinylacetyl chloride in an all-glass apparatus yielded, exactly as detailed for the methyl ester, 19 g. of ester, b. p. 143—148°/774 mm. (mainly 144—145°). Redistillation gave the pure n-*propyl vinylacetate*, b. p. 144·5°/774 mm. (Found: C, 65·7; H, 9·6. $C_7H_{12}O_2$ requires C, 65·6; H, 9·4%).

Method 2. A mixture of 38 g. of silver vinylacetate, 25 g. of pure *n*-propyl bromide, and 75 ml. of absolute ethyl alcohol was refluxed for 23 hours, poured into 400 ml. of water, saturated with pure sodium chloride, and the upper layer separated. This was washed with sodium hydrogen carbonate solution and water, dried ($CaSO_4$), and distilled: the liquid ester passed over at 138—149°. Upon redistillation from a Claisen flask with fractionating side arm, it boiled at 141—144°/754 mm. (mainly at 141·5—143·5°) and had $d_4^{20°}$ 0·9068, $n_D^{20°}$ 1·4151. The acid chloride method was superior since the resulting ester had a sharper b. p. and a lower density ($d_4^{20°}$ 0·9003, $n_D^{20°}$ 1·4150).

n-*Butyl vinylacetate*. *Method* 1. The reaction between 15·6 g. of pure, dry *n*-butyl alcohol and 20 g. of vinylacetyl chloride gave, as detailed for the methyl ester, 23 g. of pure n-*butyl vinylacetate* (Found: C, 67·5; H, 10·0. $C_8H_{14}O_2$ requires C, 67·6; H, 9·9%).

Method 2. A mixture of 38 g. of silver vinylacetate, 27 g. of pure *n*-butyl bromide, and 50 ml. of sodium-dried A.R. benzene was refluxed for 25 hours and the product isolated as described for the ethyl ester: 16 g. of *n*-butyl ester, b. p. 54—56°/9 mm., were obtained. Upon redistillation, this boiled at 58—60°/10 mm., and a middle fraction, b. p. 59°/10 mm., gave $d_4^{20°}$ 0·8965, $n_D^{20°}$ 1·42167, R_D 40·28, P (mean) 361·8. These results are in moderate agreement with those for the ester prepared from the acid chloride, but the latter procedure is to be preferred for the preparation of the pure ester.

n-*Amyl vinylacetate*. The reaction between 18·6 g. of dry *n*-amyl alcohol (Sharples, carefully fractionated) and 20 g. of vinylacetyl chloride, as detailed for the methyl ester, gave 23 g. of n-*amyl vinylacetate*, b. p. 74·5°/12 mm. (Found: C, 69·1; H, 10·3. $C_9H_{16}O_2$ requires C, 69·2; H, 10·3%).

Esters of Undecylenic Acid.—Purification of undecylenic acid. The pure commercial acid was redistilled and the fraction, b. p. 152—154°/6 mm., was collected; this had a setting point of 22·6—22·8°. A mixture of 240 g. of the redistilled acid, 430 g. of A.R. absolute methyl alcohol, and 22 g. of concentrated sulphuric acid was refluxed for 20 hours, most of the excess of methyl alcohol was distilled off from a water-bath, and the residue poured into 2 l. of water. The ester (260 g.) was separated, washed successively with saturated sodium hydrogen carbonate solution and water, dried (yield 252 g.), and distilled in two lots; the methyl undecylenate was collected at 247—250°/771 mm. (mainly at 247—249°). In a 1·5- or 2-l. round-bottomed flask were placed 300 ml. of 20% sodium hydroxide solution and 0·2 g. of "pentrone" (largely sodium oleylsulphonate), the latter to reduce the foaming during the subsequent hydrolysis. The methyl undecylenate (150 g.) was added dropwise to the warm alkali solution (if the ester is added in one lot, a very vigorous reaction sets in after a few minutes and the mixture is shot out of the flask) and reacted rapidly. When the ester layer was no longer visible, the product was carefully acidified with concentrated hydrochloric acid, allowed to cool, the acid extracted with ether, the ethereal extract dried (Na_2SO_4), and the solvent removed. The undecylenic acid was isolated by distillation: b. p. 148°/4·5 mm., 157°/6 mm.; s. p. 23·5°. Distillation of the acid at atmospheric pressure (b. p. 276—280°/756 mm.) leads to considerable loss.

Methyl undecylenate. This was prepared from the pure acid, m. p. 23·5° (1 mol.), A.R. absolute methyl alcohol (10 mols.), and concentrated sulphuric acid; b. p. 247—248°/776 mm.

Ethyl undecylenate. A mixture of 26 g. of undecylenic acid, m. p. 23·5°, 66 g. of absolute ethyl alcohol, and 3·5 g. of concentrated sulphuric acid was refluxed for 20 hours. The mixture was poured into a large excess of water, saturated with salt, the ester separated and washed successively with saturated sodium hydrogen carbonate solution and saturated salt solution, and then twice distilled. The yield of pure ester, b. p. 258—259°/761 mm., was 24 g.

n-*Propyl undecylenate*. A mixture of 23 g. of pure undecylenic acid, 15 g. of pure *n*-propyl alcohol, 25 ml. of sodium-dried A.R. benzene, and 5 g. of concentrated sulphuric acid was refluxed for 30 hours, poured into water, the benzene layer separated, washed successively with saturated sodium hydrogen carbonate solution and water, and dried. The benzene was removed at atmospheric pressure and the residue twice distilled under reduced pressure. The yield of pure n-*propyl undecylenate*, b. p. 139·5°/7 mm., was 17·5 g. (Found: C, 74·2; H, 11·9. $C_{14}H_{26}O_2$ requires C, 74·2; H, 11·6%).

n-*Butyl undecylenate*. A mixture of 23 g. of pure undecylenic acid, 19 g. of pure *n*-butyl alcohol, 25 ml. of sodium-dried A.R. benzene, and 5 g. of concentrated sulphuric acid was refluxed for 20 hours and yielded, as for the *n*-propyl ester, 17 g. of pure n-*butyl undecylenate*, b. p. 150°/6 mm. (Found: C, 75·1; H, 11·6. $C_{15}H_{28}O_2$ requires C, 75·0; H, 11·7%).

Unsaturated Aliphatic Hydrocarbons.—Pent-2-ene. This was prepared from the low-b. p. by-product obtained in the preparation of 3-bromopentane from diethylcarbinol (Sharples) by the hydrogen bromide–sulphuric acid procedure (**8**, 77). It was fractionated from excess of sodium and the portion boiling at 36—38° again fractionated from sodium; it boiled constantly at 36·3—36·4°/755 mm.

Hexene. 100 G. of *n*-hexyl alcohol, b. p. 156—157°/752 mm., were mixed with 4 g. of concentrated sulphuric acid and slowly fractionated from a three-section Pyrex Young and Thomas column; the temperature of the distillate was not allowed to rise above 90° (compare Wibaut *et al.*, *Rec. Trav. chim.*, 1939, **58**, 338). The aqueous layer in the distillate was discarded, the organic phase was washed successively with dilute sodium hydroxide solution and water, dried, and twice fractionated from sodium. The product boiled at 65·5—66°/752 mm. and consisted of a mixture of hexenes.

1-*Octene to* 1-*hexadecene*. 100 G. samples of the highly purified alkenes were kindly supplied by the Connecticut Hard Rubber Co., of 407 East Street, New Haven, Conn., U.S.A. These were dried over anhydrous calcium sulphate for several days and then fractionated; over 95% boiled at the temperatures

given below and a middle fraction was removed for the physical measurements: oct-1-ene, b. p. 120·5°/765 mm.; dec-1-ene, b. p. 169°/761 mm.; dodec-1-ene, b. p. 80°/5 mm.; tetradec-1-ene, b. p. 125°/14 mm.; hexdec-1-ene, b. p. 153°/14 mm.

Esters of Allylmalonic Acid.—Allylmalonic acid was prepared by the method of Linstead and Rydon (*J.*, 1933, 582) and was recrystallised from benzene; it had m. p. 103°. The yield of pure acid from 43·5 g. of sodium, 435 g. of absolute ethyl alcohol, 300 g. of ethyl malonate, and 234 g. of allyl bromide did not exceed 75 g.

Dimethyl allylmalonate. A mixture of 20·5 g. of allylmalonic acid, 18·5 g. of anhydrous methyl alcohol, 55 ml. of sodium-dried A.R. benzene, and 9 g. of concentrated sulphuric acid was refluxed for 21 hours, then poured into water, the benzene layer separated, washed successively with saturated sodium hydrogen carbonate solution and water, dried, and the solvent removed. Distillation yielded 16·5 g. of pure *dimethyl allylmalonate*, b. p. 206·5—207·5°/771 mm. (Found: C, 56·0; H, 6·8. $C_8H_{12}O_4$ requires C, 55·8; H, 7·1%).

Diethyl allylmalonate. A mixture of 20·5 g. of allylmalonic acid, 26 g. of absolute ethyl alcohol, 55 ml. of sodium-dried A.R. benzene, and 6 g. of concentrated sulphuric acid was refluxed for 24 hours and yielded, as for the methyl ester, 20 g. of ethyl allylmalonate, b. p. 222·5—223°/766 mm.

Di-n-propyl allylmalonate. A mixture of 15 g. of allylmalonic acid, 25 g. of pure, absolute *n*-propyl alcohol, 37·5 ml. of sodium-dried A.R. benzene, and 6 g. of concentrated sulphuric acid was refluxed for 24 hours, and afforded, as for the methyl ester, 17 g. of *di-n-propyl allylmalonate*, b. p. 121·5°/7 mm. (Found: C, 63·4; H, 8·8. $C_{12}H_{20}O_4$ requires C, 63·5; H, 9·0%).

Di-n-butyl allylmalonate. A mixture of 15 g. of allylmalonic acid, 31 g. of pure, anhydrous *n*-butyl alcohol, 37·5 ml. of sodium-dried A.R. benzene, and 6 g. of concentrated sulphuric acid was refluxed for 31 hours and yielded, after the usual procedure, 21 g. of *di-n-butyl allylmalonate*, b. p. 149·5°/8·5 mm. (Found: C, 65·6; H, 9·4. $C_{14}H_{24}O_4$ requires C, 65·6; H, 9·4%).

Allyl Esters of Aliphatic Carboxylic Acids.—Allyl acetate. A mixture of 40 g. of dry, redistilled allyl alcohol, b. p. 96·5—97°/767 mm., 97°/773 mm., 120 g. of A.R. glacial acetic acid, and 2 g. of concentrated sulphuric acid was refluxed for 20 hours, poured into excess of brine, the ester layer separated and washed successively with saturated sodium hydrogen carbonate solution and brine, dried, and distilled. The yield of allyl acetate, b. p. 104°/773 mm., was 44 g.

Allyl propionate. A mixture of 40 g. of pure anhydrous allyl alcohol, 148 g. of propionic acid (b. p. 141—142°/773 mm.), and 2 g. of concentrated sulphuric acid was refluxed for 18 hours and yielded, as for allyl acetate, 43 g. of allyl propionate, b. p. 123°/767 mm.

Allyl n-butyrate. A mixture of 40 g. of pure anhydrous allyl alcohol, 176 g. of *n*-butyric acid (b. p. 161·5—162·5°/765 mm.), and 2 g. of concentrated sulphuric acid was refluxed for 31 hours and yielded, after pouring into water, etc., 60 g. of allyl *n*-butyrate, b. p. 141—142°/747 mm.

Diallyl succinate. A mixture of 44 g. of pure, anhydrous allyl alcohol, 30 g. of A.R. succinic acid, 95 ml. of sodium-dried A.R. benzene, and 15 g. of concentrated sulphuric acid was refluxed for 22 hours and yielded, after being worked up in the usual manner and distilled twice, 26 g. of allyl succinate, b. p. 100°/0·8 mm.

Allyl Halides and Diallyl.—Allyl chloride. 87 G. of pure anhydrous allyl alcohol were added to a cold mixture of 285 g. of concentrated hydrochloric acid and 408 g. of zinc chloride sticks, and the whole refluxed for 5 hours. The crude chloride (56 g.) was isolated by distillation as for *n*-propyl chloride (VIII, **50**), and was washed successively with water, saturated sodium hydrogen carbonate solution, and water, dried ($CaSO_4$), and distilled. It boiled constantly at 45°/764 mm.

Allyl bromide. Method 1. A mixture of 58 g. of pure anhydrous allyl alcohol and 520 g. of A.R. constant-b. p. hydrobromic acid was slowly distilled from a 500-ml. distilling flask during 7 hours. The bromide layer (112 g.) in the distillate was separated, washed twice with an equal volume of concentrated hydrochloric acid (loss 4 g.), water, saturated sodium hydrogen carbonate solution, and water, dried, and distilled. The allyl bromide boiled constantly at 70°/759 mm.

Method 2. Pure allyl alcohol was converted into allyl bromide by the hydrogen bromide–sulphuric acid procedure (*Org. Synth.*, Coll. Vol. I, 1941, 27) and boiled at 69·5—72°/745 mm., mainly at 69·5—71°. This was redistilled, and a middle fraction, b. p. 70°/750 mm., collected; it had $d_4^{20°}$ 1·4314, $n_D^{20°}$ 1·4689, R_D 23·54, *P* (mean) 193·3.

Allyl iodide. A mixture of 29 g. of pure anhydrous allyl alcohol and 337 g. of constant-b. p. hydriodic acid was distilled slowly from a 500-ml. distilling flask during 7 hours. The lower layer of crude allyl iodide (83 g.) in the distillate was removed, a further 29 g. of allyl alcohol was added to the acid layer, and the distillation was repeated, a further 71 g. of crude allyl iodide being obtained. The crude iodide was washed with dilute sodium hydroxide solution, dried, and distilled from a little pure silver in the dark. The allyl iodide was collected at 100°/765 mm. and had $d_4^{20°}$ 1·7765, $n_D^{20°}$ 1·5437, whence R_D 29·84. The compound darkened considerably upon exposure to light and was too unstable for satisfactory physical measurements.

Diallyl (hexa-1 : 5-diene). 56 G. of clean sodium (small pieces) were placed in a 500-ml. round-bottomed flask fitted with two 10″ or 12″ double-surface condensers in series. 136 G. of freshly distilled allyl iodide were employed. About one-quarter of the allyl iodide was added to the sodium, and the flask gently warmed until the sodium just *commenced* to melt; the flame was then immediately removed. A vigorous reaction set in and a liquid refluxed. The remainder of the iodide was added during 2 hours. The reaction mixture was allowed to cool, and the hydrocarbon distilled off from a butyl phthalate bath at 90—100°. The yield of colourless liquid was 24 g. Upon redistillation from a little sodium, the diallyl boiled constantly at 59·5°/775 mm. and the sodium remained unattacked.

Dialkyl Maleates and Fumarates.—Maleic acid. Pure commercial maleic acid was converted into the anhydride by distillation with tetrachloroethane (Mason, *J.*, 1930, 700); the anhydride distilled at 195—197° and, after recrystallisation from chloroform, melted at 54°. This was evaporated with a little water on a water-bath and dried in a vacuum desiccator over concentrated sulphuric acid. The m. p. of the pure maleic acid depends to a marked degree upon the rate of heating and values between 133° and 143° may be observed. Slow heating (about 20 minutes) gives a value of 133—134° and more

rapid heating (*ca.* 10 minutes) 139—140°. If the acid is immersed in a bath at 140°, it melts sharply at 143°. The low m. p.s observed upon slow heating are evidently due to the formation of maleic anhydride and/or fumaric acid, which depress the m. p.

Fumaric acid. The commercial acid was recrystallised from N-hydrochloric acid, and, after drying in a vacuum desiccator over anhydrous calcium chloride and sodium hydroxide pellets, melted at 283·5° (sealed capillary tube). A further recrystallisation raised the m. p. to 286—287°.

Silver maleate. 130 G. of pure maleic acid were dissolved in 650 ml. of 3·5N-ammonia solution, and a solution containing 400 g. of silver nitrate added; the precipitated silver maleate was washed with water and dried at 40—50°. The yield was 295 g. The silver salt may also be prepared from the solution obtained by dissolving a known weight of pure maleic anhydride in water.

Silver fumarate. 100 G. of pure fumaric acid, 580 ml. of 3N-ammonia solution, and a solution of 290 g. of silver nitrate in 500 ml. of water similarly yielded 272 g. of silver fumarate.

Two methods of preparation of dialkyl maleates and fumarates were employed, *viz.*, from the silver salt and the alkyl bromide or iodide (usually in the presence of pure dry ether or benzene) and from the acid, alcohol, pure dry benzene, and concentrated sulphuric acid. Both procedures yielded identical esters as the following typical results prove.

Ester.	Method.	$d_4^{20°}$.	$n_D^{20°}$.	R_D.	P.
Me maleate	Ag salt, MeI (ether)	1·1502	1·4424	33·18	311·9
Me maleate	Acid, $CH_3{\cdot}OH$, C_6H_6, H_2SO_4	1·1512	1·4418	33·11	311·9
Et maleate	Ag salt, EtI (benzene)	1·0662	1·4402	42·58	386·7
Et maleate	Acid, $C_2H_5{\cdot}OH$, C_6H_6, H_2SO_4	1·0674	1·4402	42·58	—
Am^i maleate	Ag salt, Am^{i}Br (benzene)	0·9714	1·4459	70·35	613·0
Am^i maleate	Acid, Am^{i}OH, C_6H_6, H_2SO_4	0·9712	1·4460	70·38	613·5
Et fumarate	Ag salt, EtI (benzene)	1·0521	1·4408	43·20	389·3
Et fumarate	Acid, EtOH, C_6H_6, H_2SO_4	1·0512	1·4407	43·19	—
Am^i fumarate	Ag salt, Am^{i}Br (benzene)	0·9655	1·4479	71·06	619·5
Am^i fumarate	Acid, Am^{i}OH, C_6H_6, H_2SO_4	0·9653	1·4481	71·10	619·7

General procedure for the preparation of esters by the silver salt method. The silver salt, suspended in pure anhydrous ether (for methyl maleate only) or in sodium-dried A.R. benzene, was mixed with a slight excess of the pure alkyl bromide or iodide, and the mixture was refluxed on a water-bath for the stated number of hours. If an alkyl iodide was employed, it was first shaken mechanically with pure silver powder until colourless, since traces of iodine appear to act catalytically in the interconversion of the *cis-trans*-isomers. The mixture was filtered through a sintered-glass funnel, and the residual silver salt extracted with the solvent medium, usually benzene. Small quantities of acid by-products are formed in most preparations of esters by the silver salt method. The solution of the ester was then washed successively with saturated sodium hydrogen carbonate solution, and water, dried ($MgSO_4$ or $CaSO_4$), the solvent removed, and the ester distilled.

General procedure for the preparation of esters by the acid, alcohol, benzene, sulphuric acid method. A mixture of the pure acid, anhydrous alcohol, sodium-dried A.R. benzene, and concentrated sulphuric acid was refluxed for 10—30 hours, poured into a large volume of water, the benzene layer separated (on occasion it was advisable to extract the aqueous layer with ether and combine the ethereal extract with the benzene layer), washed with water, saturated sodium hydrogen carbonate solution and water, dried ($MgSO_4$ or $CaSO_4$), and the solvent distilled off at atmospheric pressure. Further distillation yielded the pure ester.

Methyl maleate. Method 1. A mixture of 140 g. of silver maleate, 117 g. of colourless methyl iodide, and 75 ml. of anhydrous ether was refluxed for 1 hour, and yielded 16 g. of ester, b. p. 201°/770 mm.

Method 2. A mixture of 29 g. of maleic acid, 26 g. of absolute methyl alcohol, 95 ml. of benzene, and 4 g. of concentrated sulphuric acid was refluxed for 12 hours and yielded 21 g. of ester, b. p. 202°/762 mm.

Ethyl maleate. Method 1. A mixture of 90 g. of silver maleate, 84 g. of colourless ethyl iodide, and 50 ml. of benzene was refluxed for 10 hours and afforded 26·5 g. of ester, b. p. 219·5°/758 mm.

Method 2. A mixture of 29 g. of maleic acid, 37 g. of absolute ethyl alcohol, 95 ml. of benzene, and 4 ml. of concentrated sulphuric acid was refluxed for 12 hours and yielded 26 g. of ester, b. p. 219·5°/762 mm.

n-*Propyl maleate.* A mixture of 70 g. of silver maleate, 52 g. of *n*-propyl bromide, 50 ml. of benzene, and 4 ml. of concentrated sulphuric acid was refluxed for 28 hours and afforded 25 g. of ester, b. p. 126°/12 mm.

n-*Butyl maleate.* A mixture of 70 g. of silver maleate, 61 g. of *n*-butyl bromide, and 50 ml. of benzene was refluxed for 19 hours and afforded 26·5 g. of ester, b. p. 147·5°/12 mm.

iso*Butyl maleate.* A mixture of 30 g. of maleic acid, 66 g. of *iso*butyl alcohol, 100 ml. of benzene, and 16 g. of concentrated sulphuric acid was refluxed for 35 hours and afforded 50 g. of *ester*, b. p. 125·5°/5 mm. (Found: C, 63·4; H, 8·6. $C_{12}H_{20}O_4$ requires C, 63·1; H, 8·8%).

n-*Amyl maleate.* A mixture of 70 g. of silver maleate, 66 g. of *n*-amyl bromide, and 50 ml. of benzene was refluxed for 26 hours and gave 32 g. of ester, b. p. 161°/10 mm.

iso*Amyl maleate. Method* 1. A mixture of 70 g. of silver maleate, 66 g. of *iso*amyl bromide (from Bisol fermentation alcohol), and 50 ml. of benzene was refluxed for 20 hours and yielded, after two distillations, 17 g. of ester, b. p. 157°/13 mm. There was a large high-b. p. residue in the first distillation.

Method 2. A mixture of 29 g. of maleic acid, 72 g. of Bisol fermentation *iso*amyl alcohol, 100 ml. of benzene, and 9 ml. of concentrated sulphuric acid was refluxed for 35 hours and yielded 60·5 g. of ester, b. p. 155°/10 mm. There was no high-b. p. residue.

Ethyl fumarate. Method 1. A mixture of 70 g. of silver fumarate, 70 g. of colourless ethyl iodide, and 50 ml. of benzene was refluxed for 15 hours and yielded 17 g. of ester, b. p. 214°/760 mm. If the benzene was replaced by absolue ethyl alcohol, the yield of pure ester was about 3 g.

Method 2. A mixture of 29 g. of fumaric acid, 37 g. of ethyl alcohol, 95 ml. of benzene, and 4 g. of concentrated sulphuric acid was refluxed for 12 hours and gave 30 g. of ester, b. p. 213·5°/749 mm.

n-*Propyl fumarate.* A mixture of 70 g. of silver fumarate, 52 g. of *n*-propyl bromide, and 60 ml. of benzene was refluxed for 13 hours and afforded 28 g. of ester, b. p. 110°/5 mm.

n-*Butyl fumarate.* A mixture of 70 g. of silver fumarate, 61 g. of *n*-butyl bromide, and 50 ml. of benzene was refluxed for 18 hours and yielded 26·5 g. of *ester*, b. p. 138·5°/8 mm. (Found: C, 63·4; H, 8·2. $C_{12}H_{20}O_4$ requires C, 63·1; H, 8·8%).

iso*Butyl fumarate.* A mixture of 25 g. of fumaric acid, 55 g. of *iso*butyl alcohol, 85 ml. of benzene, and 13·5 g. of concentrated sulphuric acid was refluxed for 28 hours and yielded 40 g. of ester, b. p. 122°/5 mm.

n-*Amyl fumarate.* A mixture of 70 g. of silver fumarate, 66 g. of *n*-amyl bromide, and 50 ml. of benzene was refluxed for 19 hours and afforded 31 g. of *ester*, b. p. 162°/7 mm. (Found: C, 65·6; H, 9·1. $C_{14}H_{24}O_4$ requires C, 65·6; H, 9·4%).

iso*Amyl fumarate.* *Method* 1. A mixture of 62 g. of silver fumarate, 57 g. of *iso*amyl bromide (from Bisol fermentation alcohol), and 50 ml. of benzene was refluxed for 22 hours and yielded, after two distillations, 16·5 g. of ester, b. p. 166°/11 mm. There was a large high-b. p. residue in the first distillation.

Method 2. A mixture of 29 g. of fumaric acid, 72 g. of Bisol fermentation *iso*amyl alcohol, 100 ml. of benzene, and 9 g. of concentrated sulphuric acid was refluxed for 29 hours and yielded 55·5 g. of ester, b. p. 156°/7 mm. There was no high-b. p. residue.

Dialkyl Citraconates and Mesaconates.—Citric acid was converted into itaconic anhydride (*Org. Synth.*, 1931, **11**, 71) and then successively into citraconic anhydride (*loc. cit.*, p. 29) and citraconic acid, m. p. 92—93°.

The authors were unable to confirm all the observations given in *Org. Synth.* (*loc. cit.*, p. 75) for the conversion of citraconic anhydride into mesaconic acid; in particular, red fumes were observed initially, but not at the end of the reaction, although this is regarded as an essential criterion that the rearrangement had occurred. Our observations are accordingly recorded. A mixture of 110 g. of citraconic anhydride, b. p. 91°/11 mm., 110 ml. of water, and 165 ml. of dilute nitric acid (33 ml. concentrated acid, 132 ml. water) were *slowly* evaporated in a 500-ml. Pyrex flask until solid commenced to separate (6 hours). After standing overnight, the almost solid mass was filtered off on a sintered-glass funnel and washed with a little water. The yield of crude product was 52—55 g., and upon recrystallisation from 100 ml. of water 45 g. of pure citraconic acid, m. p. 204°, were obtained. The original filtrate upon concentration yielded a further 5 g. of acid.

Methyl citraconate. A mixture of 30 g. of citraconic acid, 30 g. of methyl alcohol, 100 ml. of benzene, and 5 g. of concentrated sulphuric acid was refluxed for 36 hours and yielded 29 g. of the ester, b. p. 209·5°/764 mm.

Ethyl citraconate. A mixture of 25 g. of citraconic acid, 29 g. of ethyl alcohol, 100 ml. of benzene, and 4 g. of concentrated sulphuric acid was refluxed for 22 hours and afforded 28 g. of the ethyl ester, b. p. 228°/766 mm.

n-*Propyl citraconate.* A mixture of 25 g. of citraconic acid, 38 g. of *n*-propyl alcohol, 100 ml. of benzene, and 4 g. of concentrated sulphuric acid was refluxed for 25 hours and yielded 28 g. of the n-*propyl* ester, b. p. 112°/6 mm. (Found: C, 61·9; H, 8·2. $C_{11}H_{18}O_4$ requires C, 61·7; H, 8·5%).

Methyl mesaconate. A mixture of 30 g. of mesaconic acid, 30 g. of methyl alcohol, 100 ml. of benzene, and 5 g. of concentrated sulphuric acid was refluxed for 21 hours and yielded 22 g. of ester, b. p. 86°/6 mm. Distillation under 764 mm. gave a b. p. of 205°, but a little charred residue remained in the flask.

Ethyl mesaconate. A mixture of 25 g. of mesaconic acid, 29 g. of ethyl alcohol, 100 ml. of benzene, and 4 g. of concentrated sulphuric acid was refluxed for 24 hours and yielded 27·5 g. of ester, b. p. 95°/6 mm. The b. p. under 754 mm. is 224°, but slight decomposition occurs.

n-*Propyl mesaconate.* A mixture of 25 g. of mesaconic acid, 38 g. of *n*-propyl alcohol, 100 ml. of benzene, and 4 g. of concentrated sulphuric acid was refluxed for 24 hours and afforded 30 g. of the n-*propyl* ester, b. p. 128°/10 mm. (Found: C, 61·7; H, 8·2. $C_{11}H_{18}O_4$ requires C, 61·7; H, 8·5%).

Dialkyl Methylsuccinates.—Methylsuccinic acid. 440 G. of redistilled thionyl chloride were placed in a 1·5-l. flask fitted with a dropping-funnel and a double-surface condenser attached to a gas-absorption device. 250 G. of redistilled propionic acid were added to the warm thionyl chloride at such a rate that the mixture refluxed gently (*ca.* 1 hour); it was then refluxed for 30 minutes to remove dissolved sulphur dioxide. One g. of purified red phosphorus was added, followed by 620 g. of dry bromine during 7 hours whilst the mixture was refluxed gently. The resulting dark product was refluxed for 7 hours, *i.e.*, until evolution of hydrogen bromide almost ceased; the liquid then had a much lighter colour. The resulting crude α-bromopropionyl chloride was added during 2·5 hours to 500 ml. of absolute ethyl alcohol contained in a three-necked flask, fitted with a dropping-funnel, mechanical stirrer and reflux condenser, and cooled externally in running water. When the addition was complete, the mixture was heated on a water-bath for 4 hours (some hydrogen chloride was evolved). The reaction product was filtered into 1 l. of water, the heavy oil separated and washed successively with water, saturated sodium hydrogen carbonate solution and water, dried, and distilled. Some ethyl bromide passed over first, followed by ethyl α-bromopropionate (450 g.) at 65—67°/20 mm. (or 69—70°/25 mm.).

To a suspension of ethyl sodiocyanoacetate, prepared from a solution of 25·9 g. of sodium in 315 ml. of absolute ethyl alcohol and 128·3 g. of ethyl cyanoacetate, were added slowly 189 g. of ethyl α-bromopropionate: heat was evolved and the mixture became more fluid. The mixture was heated on a water-bath for 1 hour, poured into 1·5 l. of water, and the ester extracted several times with ether. The ethereal extract was washed with dilute sodium carbonate solution and water, dried, and distilled: the crude ethyl 1-cyano-2-methylsuccinate (145 g.) was collected at 161—176°/28 mm., chiefly at 167°/28 mm. (compare Bone and Sprankling, *J.*, 1899, **75**, 845, who give b. p. 140—165°/24 mm.). Redistillation afforded 110 g. of the pure ester, b. p. 161—166°/25 mm. (largely 163°/25 mm.). The following method of hydrolysis is superior to that described by Bone and Sprankling (*loc. cit.*). 100 G. of the pure ester were mixed with 400 ml. of concentrated hydrochloric acid and refluxed for 16 hours

whilst a stream of hydrogen chloride was passed into the liquid. The reaction product was extracted several times with ether, the extract dried, and the solvent removed: the residue was recrystallised from benzene and yielded 52 g. of pure methylsuccinic acid, m. p. 112°.

Methyl methylsuccinate. A mixture of 25 g. of methylsuccinic acid, 20 g. of methyl alcohol, 100 ml. of benzene, and 3 g. of concentrated sulphuric acid was refluxed for 20 hours and yielded 18 g. of ester, b. p. 196°/760 mm.

Ethyl methylsuccinate. A mixture of 20 g. of methylsuccinic acid, 24 g. of ethyl alcohol, 100 ml. of benzene, and 3 g. of concentrated sulphuric acid was refluxed for 24 hours and yielded 21·5 g. of ester, b. p. 217°/764 mm.

n-*Propyl methylsuccinate.* A mixture of 20 g. of methylsuccinic acid, 30 g. of *n*-propyl alcohol, 100 ml. of benzene, and 3 g. of concentrated sulphuric acid was refluxed for 24 hours and yielded 27·5 g. of the n-*propyl* ester, b. p. 246·5°/763 mm. (Found: C, 61·3; H, 9·0. $C_{11}H_{20}O_4$ requires C, 61·1; H, 9·3%).

Alkyl trans-*Crotonates.*—trans-*Crotonic acid.* Crystallisation of the commercially pure crotonic acid from organic solvents does not always give satisfactory results. The simplest procedure is to distil (say) 100 g. of the acid contained in a 100-ml. Claisen flask, using an air-bath; the pure *trans*-crotonic acid passes over at 180—182°/759 mm. and crystallises on cooling; m. p. 72—73°. The recovery is about 90%.

The esters were prepared by the silver salt method, following the general procedure described under alkyl maleates and fumarates. Methyl and ethyl crotonate were also prepared by the excess acid method, but the results for *n*-propyl crotonate by this procedure were unsatisfactory. It is noteworthy that acid by-products are formed in the silver salt method and the proportion appears to increase with the molecular weight of the alkyl radical; the washing with sodium hydrogen carbonate solution is therefore essential.

Silver crotonate. 120 G. of pure crotonic acid were dissolved in 410 ml. of 3·5N-ammonia solution, and a solution containing 240 g. of silver nitrate was added slowly and with stirring. The precipitate was filtered off, washed, and dried in a vacuum desiccator or at 40—50°. The yield was almost quantitative.

Methyl crotonate. Method 1 (excess acid procedure). 16 G. of absolute methyl alcohol were mixed with 4 g. of concentrated sulphuric acid and 80 g. of crotonic acid were added. The mixture was refluxed on a water-bath for 21 hours (a homogeneous liquid was produced within 2—3 hours) and then allowed to stand overnight, some solid separating out. The liquid portion was decanted, and the solid well washed with water; the combined liquid and washings was washed successively with water, saturated sodium hydrogen carbonate solution, and water, dried, and twice distilled. The yield of ester, b. p. 119°/768 mm., was 23 g.; some high-b. p. residue was obtained in the first distillation.

Method 2. A mixture of 100 g. of silver crotonate, 71 g. of colourless methyl iodide, and 100 ml. of anhydrous ether was refluxed for 22 hours and yielded 22·5 g. of ester, b. p. 119°/772 mm.

Ethyl crotonate. Method 1. A mixture of 16 g. of absolute ethyl alcohol and 6 g. of concentrated sulphuric acid with 60 g. of crotonic acid was refluxed for 24 hours and yielded, as for the methyl ester, 19 g. of ethyl crotonate, b. p. 136·5°/761 mm., after two distillations.

Method 2. A mixture of 65 g. of silver crotonate, 52 g. of colourless ethyl iodide, and 75 ml. of anhydrous ether was refluxed for 11 hours and afforded 18 g. of ester, b. p. 136·5°/765 mm.

n-*Propyl crotonate.* A mixture of 120 g. of silver crotonate, 74 g. of *n*-propyl bromide, and 150 ml. of pure anhydrous benzene was refluxed for 30 hours, and the solid filtered off and washed with benzene. Attempts to wash the benzene solution of the ester with saturated sodium hydrogen carbonate solution led to considerable emulsification; it was therefore washed with water, dried, and distilled, 38 g. of ester, b. p. 154—158°/764 mm., being collected. This (or its solution in ether) was washed with saturated sodium hydrogen carbonate solution and water, dried, and distilled. The yield of pure *n*-propyl crotonate, b. p. 157·5°/768 mm., was 30 g.

n-*Butyl crotonate.* A mixture of 75 g. of silver crotonate, 55 g. of *n*-butyl bromide, and 75 ml. of anhydrous benzene was refluxed for 36 hours and yielded (experimental details as for the *n*-propyl ester) 20 g. of ester, b. p. 55°/4 mm., after two distillations.

n-*Amyl crotonate.* A mixture of 75 g. of silver crotonate, 60 g. of *n*-amyl bromide, and 75 g. of anhydrous benzene was refluxed for 26 hours and yielded (as for the *n*-propyl ester—more acidic by-products were formed) 30 g. of the n-*amyl* ester, b. p. 71·5°/5 mm. (Found: C, 69·2; H, 10·3. $C_9H_{16}O_2$ requires C, 69·2; H, 10·3%).

iso*Amyl crotonate.* A mixture of 75 g. of silver crotonate, 60 g. of *iso*amyl bromide, and 75 ml. of absolute ethyl alcohol was refluxed for 40 hours. The solid was filtered off and washed with rectified spirit. The combined alcoholic solutions were poured into three times the volume of water, sodium hydrogen carbonate was added, the mixture shaken, and the ester separated, washed, dried, and twice distilled. The yield of ester, b. p. 60°/3·5 mm., was 30 g.

Alkyl Cinnamates.—Cinnamic acid. Commercial ethyl cinnamate was washed successively with 10% sodium carbonate solution and water, dried ($MgSO_4$), and distilled: the fraction, b. p. 150—151°/20 mm., was collected. 118 G. of the purified ester were treated with a solution of 100 g. of potassium hydroxide in 100 ml. of water, 250 ml. of rectified spirit were added, the mixture refluxed for 7 hours, and the alcohol distilled off. The residue was extracted with ether (to remove any unreacted ester), acidified to Congo-red with dilute sulphuric acid, and the precipitated acid filtered off, washed with water, and dried at 90°. Its m. p. was 133·5°.

Ethyl cinnamate. A mixture of 25 g. of cinnamic acid, 23 g. of absolute ethyl alcohol, 4 g. of concentrated sulphuric acid, and 100 ml. of anhydrous benzene was refluxed for 15 hours and afforded, by the usual procedure, 23·5 g. of ester, b. p. 127°/6 mm.

n-*Propyl cinnamate.* A mixture of 25 g. of cinnamic acid, 30 g. of absolute *n*-propyl alcohol, 4 g. of concentrated sulphuric acid, and 100 ml. of anhydrous benzene was refluxed for 19 hours and yielded 26·5 g. of ester, b. p. 148°/10 mm.

n-*Butyl cinnamate.* A mixture of 25 g. of cinnamic acid, 37 g. of *n*-butyl alcohol, 4 g. of concentrated

sulphuric acid, and 100 ml. of anhydrous benzene was refluxed for 20 hours and afforded 28 g. of ester, b. p. 162°/12 mm.

Physical Measurements.—**331.** *Vinylacetic acid.* B. p. 77·5°/19 mm.; M 86·09; n_C 1·42108, n_D 1·42386, n_F 1·43064, n_G 1·43575; R_C 21·60, R_D 21·73, R_F 22·03, $R_{G'}$ 22·26; $Mn_D^{20°}$ 122·58. Densities determined: $d_{4°}^{20°}$ 1·0108, $d_{4°}^{41·4°}$ 0·9895, $d_{4°}^{61·8°}$ 0·9693, $d_{4°}^{84·7°}$ 0·9470. Apparatus *A*.

(These headings apply to corresponding columns of all subsequent tables.)

t.	H.	$d_{4°}^{t°}$.	γ.	P.	t.	H.	$d_{4°}^{t°}$.	γ.	P.
14·3°	15·48	1·0164	29·46	197·3	61·9°	13·52	0·9692	24·59	197·7
18·5	15·29	1·0123	28·98	197·3	87·3	12·57	0·9444	22·23	197·9
40·9	14·38	0·9900	26·66	197·6				Mean	197·5

332. *Methyl vinylacetate.* B. p. 108°/774 mm.; M 100·11; n_C 1·40658, n_D 1·40909, n_F 1·41523, $n_{G'}$ 1·41949; R_C 26·16, R_D 26·30, R_F 26·64, $R_{G'}$ 26·89; $Mn_D^{20°}$ 141·07. Densities determined: $d_{4°}^{20°}$ 0·9413, $d_{4°}^{41·0°}$ 0·9177, $d_{4°}^{61·8°}$ 0·8947. Apparatus *A*.

16·0°	15·76	0·9458	27·91	243·3	42·3°	14·36	0·9162	24·64	243·4
19·7	15·56	0·9416	27·43	243·3	61·3	13·41	0·8949	22·47	243·6
								Mean	243·4

333. *Ethyl vinylacetate.* B. p. 124°/745 mm.; M 114·14; n_C 1·40860, n_D 1·41107, n_F 1·41705, $n_{G'}$ 1·42159; R_C 30·79, R_D 30·95, R_F 31·35, $R_{G'}$ 31·64; $Mn_D^{20°}$ 161·06. Densities determined: $d_{4°}^{20°}$ 0·9158, $d_{4°}^{40·2°}$ 0·8944, $d_{4°}^{60·7°}$ 0·8731, $d_{4°}^{85·7°}$ 0·8445. Apparatus *E*.

17·1°	12·40	0·9189	26·54	281·9	61·1°	10·62	0·8727	21·59	282·1
40·5	11·44	0·8941	23·82	282·0	87·2	9·55	0·8429	18·75	282·3
								Mean	282·1

334. n-*Propyl vinylacetate.* B. p. 144·5°/774 mm.; M 128·17; n_C 1·41250, n_D 1·41496, n_F 1·42090, $n_{G'}$ 1·42523; R_C 35·46, R_D 35·65, R_F 36·09, $R_{G'}$ 36·42; $Mn_D^{20°}$ 181·36. Densities determined: $d_{4°}^{20°}$ 0·9003, $d_{4°}^{42·0°}$ 0·8788, $d_{4°}^{60·9°}$ 0·8607, $d_{4°}^{86·1°}$ 0·8340. Apparatus *A*.

13·1°	15·90	0·9069	27·00	322·4	61·4°	13·67	0·8602	22·02	322·8
20·3	15·60	0·9000	26·29	322·5	86·9	12·41	0·8332	19·36	322·7
41·9	14·56	0·8789	23·96	322·6				Mean	322·6

335. n-*Butyl vinylacetate.* B. p. 53°/7 mm.; M 142·19; n_C 1·41784, n_D 1·42026, n_F 1·42615, $n_{G'}$ 1·43049; R_C 40·11, R_D 40·32, R_F 40·82, $R_{G'}$ 41·18; $Mn_D^{20°}$ 201·95. Densities determined: $d_{4°}^{20°}$ 0·8930, $d_{4°}^{42·6°}$ 0·8721, $d_{4°}^{60·1°}$ 0·8556, $d_{4°}^{86·5°}$ 0·8302. Apparatus *E*.

13·0°	13·03	0·8993	27·29	361·4	61·4°	11·33	0·8544	22·55	362·6
19·3	12·80	0·8936	26·64	361·5	87·2	10·32	0·8295	19·94	362·1
42·7	11·96	0·8720	24·29	362·0				Mean	361·9

336. n-*Amyl vinylacetate.* B. p. 74·5°/12 mm.; M 156·22; n_C 1·42204, n_D 1·42446, n_F 1·43036, $n_{G'}$ 1·43460; R_C 44·77, R_D 45·00, R_F 45·54, $R_{G'}$ 45·93; $Mn_D^{20°}$ 222·54. Densities determined: $d_{4°}^{20°}$ 0·8868, $d_{4°}^{41·7°}$ 0·8677, $d_{4°}^{60·7°}$ 0·8509, $d_{4°}^{87·7°}$ 0·8264. Apparatus *A*.

18·3°	16·20	0·8883	26·95	400·7	61·0°	14·34	0·8506	22·84	401·5
41·8	15·23	0·8676	24·74	401·6	87·1	13·21	0·8269	20·45	401·8
								Mean	401·4

337. *Methyl undecylenate.* B. p. 247—248°/776 mm.; M 198·30; n_C 1·43639, n_D 1·43882, n_F 1·44481, $n_{G'}$ 1·44921; R_C 58·56, R_D 58·84, R_F 59·54, $R_{G'}$ 60·05; $Mn_D^{20°}$ 285·31. Densities determined: $d_{4°}^{20°}$ 0·8861, $d_{4°}^{42·5°}$ 0·8690, $d_{4°}^{61·6°}$ 0·8541, $d_{4°}^{87·6°}$ 0·8331. Apparatus *D*.

16·1°	13·84	0·8891	30·39	523·7	43·0°	12·94	0·8686	27·76	524·0
18·4	13·72	0·8873	30·06	523·3	61·4	12·33	0·8544	26·02	524·2
28·1	13·43	0·8799	29·18	523·8	88·1	11·47	0·8327	23·59	524·8
								Mean	524·0

338. *Ethyl undecylenate.* B. p. 258—259°/761 mm.; M 212·32; n_C 1·43580, n_D 1·43822, n_F 1·44418, $n_{G'}$ 1·44859; R_C 63·15, R_D 63·45, R_F 64·20, $R_{G'}$ 64·75; $Mn_D^{20°}$ 305·36. Densities determined: $d_{4°}^{20°}$ 0·8788, $d_{4°}^{40·9°}$ 0·8625, $d_{4°}^{61·3°}$ 0·8472, $d_{4°}^{84·6°}$ 0·8270. Apparatus *A*.

13·3°	18·02	0·8840	29·83	561·3	40·7°	16·94	0·8627	27·36	562·9
16·0	17·93	0·8819	29·61	561·6	60·3	16·19	0·8480	25·71	563·8
24·5	17·58	0·8753	28·81	562·0	87·1	14·99	0·8266	23·20	563·7
								Mean	562·6

339. n-*Propyl undecylenate.* B. p. 139·5°/7 mm.; M 226·35; n_C 1·43751, n_D 1·43993, n_F 1·44587, $n_{G'}$ 1·45029; R_C 67·79, R_D 68·12, R_F 68·92, $R_{G'}$ 69·51; $Mn_D^{20°}$ 325·92. Densities determined: $d_{4°}^{20°}$ 0·8756, $d_{4°}^{42·1°}$ 0·8590, $d_{4°}^{61·7°}$ 0·8442, $d_{4°}^{85·2°}$ 0·8259. Apparatus *A*.

16·0°	18·14	0·8786	29·84	602·1	61·8°	16·21	0·8441	25·62	603·3
24·4	17·83	0·8723	29·13	602·8	87·3	15·09	0·8243	23·29	603·2
42·2	17·04	0·8589	27·41	603·0				Mean	602·9

340. n-*Butyl undecylenate.* B. p. 150°/6 mm.; M 240·37; n_C 1·44014, n_D 1·44255, n_F 1·44852, $n_{G'}$ 1·45303; R_C 72·41, R_D 72·76, R_F 73·60, $R_{G'}$ 74·24; $Mn_D^{20°}$ 346·76. Densities determined: $d_{4°}^{20°}$ 0·8751, $d_{4°}^{41·6°}$ 0·8594, $d_{4°}^{60·7°}$ 0·8446, $d_{4°}^{86·1°}$ 0·8263. Apparatus *A*.

t.	*H.*	$d_{4°}^{t°}$	*γ.*	*P.*	*t.*	*H.*	$d_{4°}^{t°}$	*γ.*	*P.*
16·2°	18·27	0·8779	30·03	641·0	61·5°	16·36	0·8440	25·86	642·2
23·7	17·93	0·8714	29·26	641·5	86·1	15·44	0·8263	23·89	643·1
41·9	17·20	0·8592	27·67	641·6				Mean	641·9

341. *Pent-2-ene.* B. p. 36·3—36·4°/755 mm.; M 70·13; n_C 1·37768, n_D 1·38003, n_F 1·38604, $n_{G'}$ 1·39053; R_C 24·70, R_D 24·83, R_F 25·18, $R_{G'}$ 25·44; $Mn_D^{20°}$ 96·62. Density determined: $d_{4°}^{20°}$ 0·6531; temperature coefficient assumed, 0·0009, as for *n*-pentane (Part IX, *loc. cit.*). Apparatus *A*.

14·8°	14·35	0·6578	17·68	218·6	23·3°	13·79	0·6501	16·79	218·7
								Mean	218·7

342. *Hex-1-ene.* B. p. 65·5°/752 mm.; M 84·12; n_C 1·38943, n_D 1·39178, n_F 1·39783, $n_{G'}$ 1·40214; R_C 29·28, R_D 29·44, R_F 29·84, $R_{G'}$ 30·12; $Mn_D^{20°}$ 117·13. Densities determined: $d_{4°}^{20°}$ 0·6804, $d_{4°}^{40·}$ ° 0·6614. Apparatus *D*.

15·5°	11·91	0·6845	20·13	260·8	20·7°	11·61	0·6798	19·49	260·4
17·9	11·73	0·6823	19·76	260·4	40·9	10·71	0·6610	17·48	260·9
								Mean	260·6

343. *Oct-1-ene.* B. p. 120·5°/765 mm.; M 112·21; n_C 1·40660, n_D 1·40899, n_F 1·41495, $n_{G'}$ 1·41940; R_C 38·55, R_D 38·76, R_F 39·25, $R_{G'}$ 39·62; $Mn_D^{20°}$ 158·10. Densities determined: $d_{4°}^{20°}$ 0·7158, $d_{4°}^{39·7°}$ 0·7001, $d_{4°}^{60·1°}$ 0·6826, $d_{4°}^{87·0°}$ 0·6611. Apparatus *E*.

16·0°	13·34	0·7191	22·34	339·3	60·9°	11·25	0·6819	17·86	338·5
18·2	13·20	0·7173	22·05	339·0	87·0	10·16	0·6611	15·64	337·6
40·5	12·31	0·6995	20·05	339·4				Mean	338·8

344. *Dec-1-ene.* B. p. 169°/761 mm.; M 140·18; n_C 1·41936, n_D 1·42176, n_F 1·42767, $n_{G'}$ 1·43227; R_C 47·74, R_D 47·96, R_F 48·57, $R_{G'}$ 49·03; $Mn_D^{20°}$ 199·31. Densities determined: $d_{4°}^{20°}$ 0·7421, $d_{4°}^{39·8°}$ 0·7269, $d_{4°}^{59·7°}$ 0·7123, $d_{4°}^{86·8°}$ 0·6916. Apparatus *E*.

16·6°	14·14	0·7448	24·53	418·9	61·0°	12·28	0·7113	20·34	418·5
19·5	14·01	0·7425	24·23	418·9	87·3	11·25	0·6908	18·10	418·6
40·3	13·11	0·7265	22·18	418·8				Mean	418·7

345. *Dodec-1-ene.* B. p. 80°/5 mm.; M 168·31; n_C 1·42783, n_D 1·43023, n_F 1·43624, $n_{G'}$ 1·44060; R_C 56·95, R_D 57·22, R_F 57·92, $R_{G'}$ 58·43; $Mn_D^{20°}$ 240·72. Densities determined: $d_{4°}^{20°}$ 0·7601, $d_{4°}^{40·6°}$ 0·7450, $d_{4°}^{59·8°}$ 0·7315, $d_{4°}^{86·8°}$ 0·7121. Apparatus *E*.

19·2°	14·60	0·7607	25·87	499·0	59·5°	12·96	0·7317	22·10	498·7
41·7	13·64	0·7442	23·64	498·7	87·2	11·93	0·7116	19·77	498·8
								Mean	498·8

346. *Tetradec-1-ene.* B. p. 125°/14 mm.; M 196·36; n_C 1·43428, n_D 1·43670, n_F 1·44268, $n_{G'}$ 1·44716; R_C 66·23, R_D 66·55, R_F 67·34, $R_{G'}$ 67·94; $Mn_D^{20°}$ 282·11. Densities determined: $d_{4°}^{20°}$ 0·7726, $d_{4°}^{40·9°}$ 0·7581, $d_{4°}^{61·4°}$ 0·7440, $d_{4°}^{86·8°}$ 0·7271. Apparatus *E*.

21·1°	14·88	0·7718	26·75	578·6	62·3°	13·39	0·7434	23·18	579·6
40·4	14·23	0·7584	25·13	579·7	86·3	12·56	0·7274	21·28	579·8
								Mean	579·4

347. *Hexadec-1-ene.* B. p. 153°/14 mm.; M 224·22; n_C 1·43888, n_D 1·44130, n_F 1·44726, $n_{G'}$ 1·45159; R_C 75·43, R_D 75·79, R_F 76·69, $R_{G'}$ 77·32; $Mn_D^{20°}$ 323·46. Densities determined: $d_{4°}^{20°}$ 0·7824, $d_{4°}^{41·4°}$ 0·7677, $d_{4°}^{60·8°}$ 0·7545, $d_{4°}^{85·7°}$ 0·7378. Apparatus *E*.

18·9°	15·31	0·7831	27·92	658·8	61·5°	13·80	0·7540	24·23	660·4
40·8	14·60	0·7681	26·12	660·5	86·5	12·99	0·7372	22·30	661·7
								Mean	660·3

348. *Methyl allylmalonate.* B. p. 206·5—207·5°/771 mm.; M 172·18; n_C 1·43224, n_D 1·43475, n_F 1·44088, $n_{G'}$ 1·44548; R_C 41·73, R_D 41·95, R_F 42·46, $R_{G'}$ 42·84; $Mn_D^{20°}$ 247·04. Densities determined: $d_{4°}^{20°}$ 1·0707, $d_{4°}^{41·9°}$ 1·0487, $d_{4°}^{61·9°}$ 1·0288, $d_{4°}^{85·1°}$ 1·0060. Apparatus *A*.

14·5°	16·46	1·0762	33·17	384·0	42·3°	15·31	1·0484	30·06	384·5
19·3	16·28	1·0714	32·66	384·2	62·6	14·50	1·0281	27·91	384·9
27·2	16·01	1·0635	31·88	384·7	86·3	13·51	1·0048	25·42	384·8
								Mean	384·5

349. *Ethyl allylmalonate.* B. p. 222·5—223°/766 mm.; *M* 200·23; n_C 1·42806, n_D 1·43048, n_F 1·43642, $n_{G'}$ 1·44080; R_C 51·02, R_D 51·27, R_F 51·88, $R_{G'}$ 52·34; $Mn_D^{20°}$ 286·43. Densities determined: $d_4^{20°}$ 1·0098, $d_4^{41·9°}$ 0·9889, $d_4^{61·0°}$ 0·9710, $d_4^{85·5°}$ 0·9465. Apparatus *A*.

t.	*H.*	$d_{4°}^{t°}$.	γ.	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	γ.	*P.*
18·8°	15·77	1·0109	29·85	463·0	60·4°	13·99	0·9716	25·45	462·9
22·8	15·60	1·0071	29·42	463·0	86·2	13·05	0·9468	23·14	463·8
41·5	14·79	0·9893	27·40	463·1				Mean	463·2

350. n-*Propyl allylmalonate.* B. p. 121·5°/7 mm.; *M* 228·28; n_C 1·43189, n_D 1·43430, n_F 1·44020, $n_{G'}$ 1·44464; R_C 60·26, R_D 60·55, R_F 61·27, $R_{G'}$ 61·80; $Mn_D^{20°}$ 327·42. Densities determined: $d_4^{20°}$ 0·9824, $d_4^{40·6°}$ 0·9640, $d_4^{61·1°}$ 0·9454, $d_4^{86·9°}$ 0·9225. Apparatus *D*.

20·3°	12·13	0·9821	29·42	541·3	61·9°	10·82	0·9447	25·24	541·6
40·6	11·50	0·9640	27·38	541·7	86·7	10·15	0·9227	23·13	542·6
								Mean	541·8

351. n-*Butyl allylmalonate.* B. p. 149·5°/8·5 mm.; *M* 256·33; n_C 1·43477, n_D 1·43716, n_F 1·44304, $n_{G'}$ 1·44745; R_C 69·50, R_D 69·83, R_F 70·64, $R_{G'}$ 71·26; $Mn_D^{20°}$ 368·40. Densities determined: $d_4^{20°}$ 0·9621, $d_4^{41·2°}$ 0·9456, $d_4^{61·4°}$ 0·9286, $d_4^{85·5°}$ 0·9083. Apparatus *A*.

14·4°	16·30	0·9666	29·50	618·1	41·2°	15·32	0·9456	27·13	618·6
18·1	16·09	0·9636	29·03	618·9	61·5	14·54	0·9285	25·28	619·0
27·0	15·89	0·9565	28·46	619·0	86·5	13·61	0·9075	23·13	619·4
								Mean	618·8

352. *Allyl acetate.* B. p. 104°/773 mm.; *M* 100·11; n_C 1·40150, n_D 1·40396, n_F 1·41001, $n_{G'}$ 1·41445; R_C 26·25, R_D 26·39; R_F 26·74, $R_{G'}$ 26·99; $Mn_D^{20°}$ 140·55. Densities determined: $d_4^{20°}$ 0·9277, $d_4^{43·5°}$ 0·9042, $d_4^{61·4°}$ 0·8818. Apparatus *D*.

20·9°	11·47	0·9267	26·25	244·5	41·4°	10·72	0·9054	23·97	244·8
21·6	11·42	0·9260	26·12	244·4	60·5	9·85	0·8828	21·47	244·4
28·0	11·19	0·9190	25·40	244·5				Mean	244·5

353. *Allyl propionate.* B. p. 123°/767 mm.; *M* 114·14; n_C 1·40805, n_D 1·41048, n_F 1·41643, $n_{G'}$ 1·42084; R_C 30·81, R_D 30·97, R_F 31·36, $R_{G'}$ 31·66; $Mn_D^{20°}$ 161·00. Densities determined: $d_4^{20°}$ 0·9140, $d_4^{41·7°}$ 0·8923, $d_4^{60·4°}$ 0·8718, $d_4^{85·1°}$ 0·8442. Apparatus *A*.

15·3°	11·85	0·9189	26·89	282·9	40·8°	10·90	0·8932	24·04	283·0
18·7	11·68	0·9157	26·41	282·6	61·9	10·10	0·8702	21·71	283·1
25·6	11·49	0·9082	25·77	283·2	85·3	9·13	0·8440	19·03	282·8
								Mean	282·9

354. *Allyl* n-*butyrate.* B. p. 141·5—142°/747 mm.; *M* 128·17; n_C 1·41332, n_D 1·41576, n_F 1·42176, $n_{G'}$ 1·42631; R_C 35·46, R_D 35·65, R_F 36·10, $R_{G'}$ 36·44; $Mn_D^{20°}$ 181·46. Densities determined: $d_4^{20°}$ 0·9017, $d_4^{41·6°}$ 0·8797, $d_4^{60·2°}$ 0·8607, $d_4^{84·7°}$ 0·8356. Apparatus *D*.

14·4°	11·92	0·9075	26·71	321·1	61·1°	10·29	0·8598	21·88	322·3
19·2	11·77	0·9025	26·23	321·4	86·1	9·35	0·8342	19·26	321·9
41·1	11·00	0·8796	23·90	322·2				Mean	321·8

355. *Allyl succinate.* B. p. 100°/0·8 mm.; *M* 198·21; n_C 1·44890, n_D 1·45167, n_F 1·45856, $n_{G'}$ 1·46384; R_C 50·56, R_D 50·85, R_F 51·52, $R_{G'}$ 52·02; $Mn_D^{20°}$ 287·74. Densities determined: $d_4^{20°}$ 1·0510, $d_4^{41·0°}$ 1·0321, $d_4^{61·3°}$ 1·0128, $d_4^{86·2°}$ 0·9890. Apparatus *A*.

20·1°	17·12	1·0509	33·69	454·4	61·0°	15·44	1·0131	29·29	455·1
28·4	16·83	1·0433	32·88	454·9	87·3	14·43	0·9880	26·70	456·0
40·9	16·30	1·0322	31·51	454·9				Mean	454·9

356. *Allyl chloride.* B. p. 45°/764 mm.; *M* 76·53; n_C 1·41282, n_D 1·41566, n_F 1·42272, $n_{G'}$ 1·42807; R_C 20·30, R_D 20·42, R_F 20·73, $R_{G'}$ 20·96; $Mn_D^{20°}$ 108·34. Densities determined: $d_4^{20°}$ 0·9397, $d_4^{12·3°}$ 0·9469. Apparatus *A*.

10·2°	13·82	0·9493	24·57	179·6	23·8°	13·22	0·9361	23·17	179·6
20·5	13·43	0·9392	23·62	179·7				Mean	179·6

357. *Allyl bromide.* B. p. 70°/759 mm.; *M* 120·99; n_C 1·46582, n_D 1·46968, n_F 1·47933, $n_{G'}$ 1·48692; R_C 23·40, R_D 23·57, R_F 23·98, $R_{G'}$ 24·30; $Mn_D^{20°}$ 177·82. Densities determined: $d_4^{20°}$ 1·4316, $d_4^{41·1°}$ 1·3920, $d_4^{86·0°}$ 1·3655. Apparatus *A*.

11·9°	10·34	1·4466	28·01	192·4	41·2°	9·26	1·3918	24·13	192·9
15·4	10·21	1·4402	27·53	192·4	54·5	8·86	1·3683	22·70	193·4
21·9	9·97	1·4281	26·66	192·5				Mean	192·7

358. *Diallyl* (*hexa*-1 : 5-*diene*). B. p. 59·5°/775 mm.; M 82·14; n_C 1·39963, n_D 1·40248, n_F 1·40957, $n_{G'}$ 1·41505; R_C 28·85, R_D 29·04, R_F 29·49, $R_{G'}$ 29·84; $Mn_D^{20°}$ 115·20. Densities determined: $d_{4°}^{20°}$ 0·6896, $d_{4°}^{41·8°}$ 0·6678. Apparatus *D*.

t.	*H.*	$d_{4°}^{t°}$.	*γ.*	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	*γ.*	*P.*
12·4°	11·38	0·6972	19·59	248·1	23·9°	10·97	0·6857	18·58	249·0
14·3	11·31	0·6953	19·42	248·0	43·1	10·00	0·6665	16·46	248·9
19·8	11·12	0·6898	18·94	248·4				Mean	248·6

359. *Methyl maleate.* (i) From silver salt. B. p. 201°/770 mm.; M 144·12; n_C 1·43936, n_D 1·44235, n_F 1·44975, $n_{G'}$ 1·45575; R_C 32·99, R_D 33·18, R_F 33·66, $R_{G'}$ 34·05; $Mn_D^{20°}$ 207·88. Densities determined: $d_{4°}^{20°}$ 1·1502, $d_{4°}^{41·7°}$ 1·1287, $d_{4°}^{60·3°}$ 1·1096, $d_{4°}^{85·4°}$ 1·0827. Apparatus *A*.

21·0°	17·71	1·1492	38·11	311·6	61·9°	16·01	1·1080	33·22	312·3
42·0	16·82	1·1284	35·54	311·8	87·1	14·86	1·0810	30·08	311·9
								Mean	311·9

(ii) From acid. B. p. 202°/762 mm.; n_C 1·43884, n_D 1·44179, n_F 1·44915, $n_{G'}$ 1·45487; R_C 32·91, R_D 33·11, R_F 33·59, $R_{G'}$ 33·96; $Mn_D^{20°}$ 207·79. Densities determined: $d_{4°}^{20°}$ 1·1512, $d_{4°}^{40·5°}$ 1·1311, $d_{4°}^{59·4°}$ 1·1107, $d_{4°}^{85·3°}$ 1·0839. Apparatus *D*.

20·1°	13·47	1·1511	38·29	311·4	62·1°	12·10	1·1079	33·11	312·0
23·3	13·37	1·1478	37·90	311·5	87·2	11·27	1·0819	30·11	312·0
40·8	12·80	1·1308	35·75	311·6				Mean	311·9

360. *Ethyl maleate.* (i) From silver salt. B. p. 219·5°/758 mm.; M 172·18; n_C 1·43733, n_D 1·44018, n_F 1·44728, $n_{G'}$ 1·45272; R_C 42·33, R_D 42·58, R_F 43·17, $R_{G'}$ 43·62; $Mn_D^{20°}$ 247·97. Densities determined: $d^{19°}$ 1·0662, $d_{4°}^{41·6°}$ 1·0456, $d_{4°}^{60·6°}$ 1·0253, $d_{4°}^{85·1°}$ 1·0014. Apparatus *D*.

13·4°	12·57	1·0728	33·30	385·6	61·5°	11·11	1·0244	28·11	387·0
18·2	12·47	1·0680	32·89	386·1	86·6	10·45	1·0009	25·82	387·7
41·5	11·72	1·0451	30·25	386·9				Mean	386·7

(ii) From acid. This had b. p. 219·5°/762 mm.; $d_{4°}^{20°}$ 1·0674; $n_D^{20°}$ 1·44018.

361. n-*Propyl maleate.* B. p. 126°/12 mm.; M 200·23; n_C 1·44054, n_D 1·44335, n_F 1·45016, $n_{G'}$ 1·45540; R_C 51·56, R_D 51·86, R_F 52·54, $R_{G'}$ 53·07; $Mn_D^{20°}$ 229·01. Densities determined: $d_{4°}^{20°}$ 1·0245, $d_{4°}^{40·8°}$ 1·0056, $d_{4°}^{61·2°}$ 0·9870, $d_{4°}^{86·5°}$ 0·9635. Apparatus *A*.

18·7°	16·70	1·0257	32·07	464·6	62·0°	15·00	0·9863	27·70	465·7
26·3	16·53	1·0188	31·53	465·7	86·8	14·06	0·9632	25·36	466·5
41·6	15·73	1·0049	29·60	464·8				Mean	465·5

362. n-*Butyl maleate.* B. p. 147·5°/12 mm.; M 228·28; n_C 1·44270, n_D 1·44541, n_F 1·45206, $n_{G'}$ 1·45716; R_C 60·86, R_D 61·18, R_F 61·98, $R_{G'}$ 62·58; $Mn_D^{20°}$ 329·96. Densities determined: $d_{4°}^{20°}$ 0·9938, $d_{4°}^{41·6°}$ 0·9770, $d_{4°}^{60·9°}$ 0·9607, $d_{4°}^{86·9°}$ 0·9376. Apparatus *A*.

23·3°	16·38	0·9912	30·40	540·8	60·4°	15·03	0·9611	27·05	542·9
41·0	15·88	0·9775	29·07	542·3	86·9	14·24	0·9376	25·00	544·4
								Mean	542·6

363. iso*Butyl maleate.* B. p. 125·5°/6 mm.; M 228·28; n_C 1·43908, n_D 1·44184, n_F 1·44865, $n_{G'}$ 1·45392; R_C 61·16, R_D 61·48, R_F 62·32, $R_{G'}$ 62·94; $Mn_D^{20°}$ 329·13. Densities determined: $d_{4°}^{20°}$ 0·9820, $d_{4°}^{42·3°}$ 0·9642, $d_{4°}^{61·1°}$ 0·9480, $d_{4°}^{86·5°}$ 0·9265. Apparatus *A*.

21·4°	15·62	0·9809	28·69	538·6	61·1°	14·22	0·9480	25·24	539·7
25·7	15·46	0·9773	28·29	538·7	86·4	13·35	0·9264	23·16	540·6
41·0	14·94	0·9653	27·00	539·1				Mean	539·3

364. n-*Amyl maleate.* B. p. 161°/10 mm.; M 256·33; n_C 1·44489, n_D 1·44756, n_F 1·45410, $n_{G'}$ 1·45888; R_C 70·02, R_D 70·38, R_F 71·27, $R_{G'}$ 71·92; $Mn_D^{20°}$ 371·06. Densities determined: $d_{4°}^{20°}$ 0·9741, $d_{4°}^{41·4°}$ 0·9576, $d_{4°}^{61·8°}$ 0·9413, $d_{4°}^{87·0°}$ 0·9205. Apparatus *D*.

17·2°	12·89	0·9763	31·06	619·9	62·1°	11·69	0·9408	27·16	622·0
24·5	12·65	0·9705	30·39	619·8	87·3	11·01	0·9203	25·02	623·0
41·7	12·25	0·9574	28·96	621·1				Mean	621·2

365. iso*Amyl maleate.* (i) From silver salt. B. p. 157°/13 mm.; M 256·33; n_C 1·44322, n_D 1·44591, n_F 1·45244, $n_{G'}$ 1·45742; R_C 69·98, R_D 70·35, R_F 71·24, $R_{G'}$ 71·92; $Mn_D^{20°}$ 370·63. Densities determined: $d_{4°}^{20°}$ 0·9714, $d_{4°}^{41·0°}$ 0·9551, $d_{4°}^{61·1°}$ 0·9389, $d_{4°}^{86·6°}$ 0·9176. Apparatus *D*.

19·3°	11·89	0·9708	28·51	610·1	62·5°	11·02	0·9378	25·52	614·4
41·5	11·41	0·9553	26·92	611·2	86·4	10·46	0·9178	23·71	616·3
								Mean	613·0

(ii) From acid. B. p. 155°/10 mm.; n_C 1·44334, n_D 1·44601, n_F 1·45254, $n_{G'}$ 1·45747; R_C 70·01, R_D 70·38, R_F 71·27, $R_{G'}$ 71·95; $Mn_D^{20°}$ 370·65. Densities determined: $d_{4°}^{20°}$ 0·9712, $d_{4°}^{40·5°}$ 0·9549, $d_{4°}^{60·7°}$ 0·9394, $d_{4°}^{85·0°}$ 0·9181. Apparatus *D*.

t.	*H.*	$d_{4°}^{t°}$.	*γ.*	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	*γ.*	*P.*
24·5°	11·90	0·9676	28·44	611·8	60·9°	11·16	0·9392	25·65	614·2
41·4	11·44	0·9542	26·96	612·1	88·2	10·36	0·9155	23·42	616·0
								Mean	613·5

366. *Ethyl fumarate.* (i) From silver salt. B. p. 214°/760 mm.; *M* 172·18; n_C 1·43764, n_D 1·44083, n_F 1·44881, $n_{G'}$ 1·45497; R_C 42·92, R_D 43·20, R_F 43·88, $R_{G'}$ 44·40; $Mn_D^{20°}$ 248·08. Densities determined: $d_{4°}^{20°}$ 1·0521, $d_{4°}^{41·5°}$ 1·0304, $d_{4°}^{60·7°}$ 1·0110, $d_{4°}^{86·9°}$ 0·9844. Apparatus *A*.

15·9°	16·26	1·0562	32·16	388·2	61·2°	14·45	1·0105	27·34	389·6
24·9	16·04	1·0472	31·45	389·4	86·9	13·45	0·9844	24·79	390·2
41·6	15·25	1·0303	29·42	389·2				Mean	389·3

(ii) From acid. This had b. p. 213·5°/749 mm.; $d_{4°}^{20°}$ 1·0512, $n_D^{20°}$ 1·44068.

367. n-*Propyl fumarate.* B. p. 110°/5 mm.; *M* 200·23; n_C 1·44089, n_D 1·44395, n_F 1·45165, $n_{G'}$ 1·45768; R_C 52·19, R_D 52·51, R_F 53·30, $R_{G'}$ 53·91; $Mn_D^{20°}$ 289·13. Densities determined: $d_{4°}^{20°}$ 1·0129, $d_{4°}^{41·4°}$ 0·9924, $d_{4°}^{61·4°}$ 0·9744, $d_{4°}^{86·5°}$ 0·9506. Apparatus *A*.

14·1°	16·57	1·0184	31·60	466·2	41·1°	15·50	0·9927	28·81	467·3
18·6	16·44	1·0142	31·22	466·7	62·2	14·75	0·9736	26·89	468·3
24·1	16·22	1·0090	30·65	466·9	86·1	13·90	0·9510	24·75	469·6
								Mean	467·5

368. n-*Butyl fumarate.* B. p. 138·5°/5 mm.; *M* 228·28; n_C 1·44395, n_D 1·44691, n_F 1·45433, $n_{G'}$ 1·46026; R_C 61·44, R_D 61·79, R_F 62·68; $R_{G'}$ 63·39; $Mn_D^{20°}$ 330·30. Densities determined: $d_{4°}^{20°}$ 0·9869, $d_{4°}^{42·5°}$ 0·9675, $d_{4°}^{61·3°}$ 0·9513, $d_{4°}^{86·3°}$ 0·9513. Apparatus *A*.

16·5°	16·73	0·9899	31·01	544·2	42·1°	15·79	0·9678	28·61	545·5
17·9	16·64	0·9887	30·81	544·0	60·2	15·17	0·9522	27·05	546·7
22·6	16·65	0·9847	30·70	545·7	87·4	14·23	0·9296	24·77	547·8
								Mean	545·8

369. iso*Butyl fumarate.* B. p. 122°/5 mm.; *M* 228·28; n_C 1·44019, n_D 1·44315, n_F 1·45053, $n_{G'}$ 1·45635; R_C 61·67, R_D 62·03, R_F 62·92, $R_{G'}$ 63·63; $Mn_D^{20°}$ 329·45. Densities determined: $d_{4°}^{20°}$ 0·9760, $d_{4°}^{42·0°}$ 0·9581, $d_{4°}^{61·1°}$ 0·9410, $d_{4°}^{87·0°}$ 0·9182. Apparatus *D*.

20·3°	11·99	0·9758	28·89	542·4	61·7°	10·94	0·9405	25·41	544·9
23·1	11·91	0·9734	28·63	542·5	87·9	10·19	0·9176	23·09	545·3
41·6	11·46	0·9584	27·12	543·6				Mean	543·7

370. n-*Amyl fumarate.* B. p. 162°/7 mm.; *M* 256·33; n_C 1·44669, n_D 1·44962, n_F 1·45685, $n_{G'}$ 1·46256; R_C 70·70, R_D 71·10, R_F 72·10, $R_{G'}$ 72·87; $Mn_D^{20°}$ 371·58. Densities determined: $d_{4°}^{20°}$ 0·9681, $d_{4°}^{41·6°}$ 0·9510, $d_{4°}^{60·0°}$ 0·9361, $d_{4°}^{85·6°}$ 0·9147. Apparatus *D*.

15·3°	12·92	0·9719	31·01	622·4	42·3°	12·19	0·9504	28·61	623·8
19·5	12·82	0·9685	30·66	622·8	62·1	11·73	0·9344	27·08	625·8
22·8	12·72	0·9659	30·34	622·9	86·6	11·04	0·9139	24·92	626·6
								Mean	624·1

371. iso*Amyl fumarate.* (i) From silver salt. B. p. 166°/11 mm.; *M* 256·33; n_C 1·44501, n_D 1·44791, n_F 1·45518, $n_{G'}$ 1·46092; R_C 70·66, R_D 71·06, R_F 72·06, $R_{G'}$ 72·84; $Mn_D^{20°}$ 371·14. Densities determined: $d_{4°}^{20°}$ 0·9655, $d_{4°}^{41·8°}$ 0·9483, $d_{4°}^{60·5°}$ 0·9326, $d_{4°}^{86·5°}$ 0·9127. Apparatus *A*.

24·4°	16·06	0·9620	28·93	618·0	63·2°	14·73	0·9304	25·66	620·1
41·4	15·41	0·9486	27·37	618·1	86·3	13·87	0·9125	23·70	619·8
								Mean	619·5

(ii) From acid. B. p. 156°/7 mm.; n_C 1·44515, n_D 1·44806, n_F 1·45530, $n_{G'}$ 1·46098; R_C 70·70, R_D 71·10, R_F 72·09, $R_{G'}$ 72·87; $Mn_D^{20°}$ 371·19. Densities determined: $d_{4°}^{20°}$ 0·9653, $d_{4°}^{41·6°}$ 0·9487, $d_{4°}^{61·3°}$ 0·9320, $d_{4°}^{85·3°}$ 0·9125. Apparatus *A*.

21·8°	16·17	0·9639	29·19	618·1	61·0°	14·85	0·9322	25·92	620·4
28·2	16·01	0·9587	28·74	619·1	87·3	13·99	0·9109	23·86	621·9
41·3	15·48	0·9485	27·49	618·8				Mean	619·7

372. *Methyl citraconate.* B. p. 209·5°/764 mm.; *M* 158·15; n_C 1·44474, n_D 1·44781, n_F 1·45559, $n_{G'}$ 1·46170; R_C 37·83, R_D 38·06, R_F 38·66, $R_{G'}$ 39·08; $Mn_D^{20°}$ 228·97. Densities determined: $d_{4°}^{20°}$ 1·1119, $d_{4°}^{42·2°}$ 1·0894, $d_{4°}^{62·3°}$ 1·0694, $d_{4°}^{87·1°}$ 1·0442. Apparatus *D*.

19·3°	13·28	1·1126	36·49	349·4	62·0°	11·80	1·0697	31·17	349·3
28·3	13·00	1·1036	35·43	349·6	87·7	10·96	1·0436	28·25	349·4
41·3	12·49	1·0903	33·63	349·3				Mean	349·4

373. *Ethyl citraconate.* B. p. 228°/766 mm.; M 186·20; n_C 1·44115, n_D 1·44405, n_F 1·45134, $n_{G'}$ 1·45696; R_C 47·25, R_D 47·52, R_F 48·19, $R_{G'}$ 48·71; $Mn_D^{20°}$ 268·89. Densities determined: $d_{4°}^{20°}$ 1·0410, $d_{4°}^{40·6°}$ 1·0232, $d_{4°}^{61·5°}$ 1·0041, $d_{4°}^{87·5°}$ 0·9801. Apparatus *A*.

t.	*H.*	$d_{4°}^{t°}$.	γ.	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	γ.	*P.*
21·1°	16·48	1·0400	32·09	426·1	60·5°	14·89	1·0050	28·02	426·3
41·2	15·65	1·0227	29·97	426·0	87·0	13·85	0·9805	25·43	426·4
								Mean	426·2

374. n-*Propyl citraconate.* B. p. 112°/6 mm.; M 214·25; n_C 1·44341, n_D 1·44626, n_F 1·45337, $n_{G'}$ 1·45899; R_C 56·39, R_D 56·71, R_F 57·49, $R_{G'}$ 58·11; $Mn_D^{20°}$ 309·87. Densities determined: $d_{4°}^{20°}$ 1·0080, $d_{4°}^{41·6°}$ 0·9883, $d_{4°}^{61·0°}$ 0·9711, $d_{4°}^{85·6°}$ 0·9492. Apparatus *D*.

20·1°	12·51	1·0079	31·14	502·1	62·2°	11·25	0·9700	26·95	503·2
27·8	12·33	1·0010	30·48	502·9	85·7	10·64	0·9491	24·94	504·5
41·3	11·82	0·9886	28·86	502·3				Mean	503·0

375. *Methyl mesaconate.* B. p. 86°/6 mm.; M 158·15; n_C 1·45128, n_D 1·45472, n_F 1·46356, $n_{G'}$ 1·47068; R_C 38·06, R_D 38·31, R_F 38·95, $R_{G'}$ 39·47; $Mn_D^{20°}$ 230·06. Densities determined: $d_{4°}^{20°}$ 1·1195, $d_{4°}^{40·0°}$ 1·0999, $d_{4°}^{59·5°}$ 1·0793, $d_{4°}^{83·5°}$ 1·0533. Apparatus *D*.

18·9°	12·77	1·1206	35·34	344·1	60·4°	11·40	1·0784	30·36	344·2
25·3	12·66	1·1142	34·84	344·8	85·8	10·63	1·0510	27·59	344·9
40·5	12·06	1·0994	32·74	344·1				Mean	344·4

376. *Ethyl mesaconate.* B. p. 95°/6 mm.; M 186·20; n_C 1·44485, n_D 1·44806, n_F 1·45620, $n_{G'}$ 1·46261; R_C 47·50, R_D 47·80, R_F 48·54, $R_{G'}$ 49·13; $Mn_D^{20°}$ 269·64. Densities determined: $d_{4°}^{20°}$ 1·0429, $d_{4°}^{41·1°}$ 1·0233, $d_{4°}^{61·5°}$ 1·0039, $d_{4°}^{86·9°}$ 0·9784. Apparatus *D*.

20·1°	12·27	1·0428	31·60	423·3	61·2°	11·01	1·0042	27·30	423·9
24·1	12·16	1·0390	31·20	423·6	87·2	10·26	0·9781	24·78	424·8
41·2	11·55	1·0232	29·19	423·0				Mean	423·7

377. n-*Propyl mesaconate.* B. p. 128°/10 mm.; M 214·25; n_C 1·44725, n_D 1·45037, n_F 1·45823, $n_{G'}$ 1·46453; R_C 56·77, R_D 57·11, R_F 57·96, $R_{G'}$ 58·65; $Mn_D^{20°}$ 310·75. Densities determined: $d_{4°}^{20°}$ 1·0090, $d_{4°}^{40·9°}$ 0·9899, $d_{4°}^{59·0°}$ 0·9739, $d_{4°}^{86·7°}$ 0·9483. Apparatus *A*.

16·3°	16·51	1·0123	31·30	500·6	59·8°	14·87	0·9732	27·10	502·3
18·4	16·44	1·0104	31·10	500·8	86·0	13·90	0·9489	24·70	503·3
40·9	15·57	0·9899	28·86	501·6				Mean	501·7

378. *Methyl methylsuccinate.* B. p. 196°/760 mm.; M 160·17; n_C 1·41747, n_D 1·41956, n_F 1·42460, $n_{G'}$ 1·42825; R_C 37·49, R_D 37·66, R_F 38·05, $R_{G'}$ 38·34; $Mn_D^{20°}$ 227·38. Densities determined: $d_{4°}^{20°}$ 1·0755, $d_{4°}^{39·6°}$ 1·0558, $d_{4°}^{59·8°}$ 1·0360, $d_{4°}^{85·6°}$ 1·0096. Apparatus *A*.

22·1°	16·40	1·0734	32·96	357·5	60·6°	14·76	1·0352	28·61	357·9
25·1	16·34	1·0704	32·75	358·0	93·7	13·41	1·0015	25·15	358·1
40·2	15·67	1·0552	30·96	358·1				Mean	357·9

379. *Ethyl methylsuccinate.* B. p. 217°/764 mm.; M 188·22; n_C 1·41667, n_D 1·41876, n_F 1·42380, $n_{G'}$ 1·42701; R_C 46·87, R_D 47·07, R_F 47·56, $R_{G'}$ 47·88; $Mn_D^{20°}$ 267·05. Densities determined: $d_{4°}^{20°}$ 1·0094, $d_{4°}^{42·2°}$ 0·9896, $d_{4°}^{62·1°}$ 0·9702, $d_{4°}^{86·2°}$ 0·9464. Apparatus *D*.

22·4°	11·92	1·0072	29·65	436·1	61·0°	10·72	0·9712	25·71	436·4
24·4	11·82	1·0057	29·36	435·7	87·3	9·98	0·9454	23·30	437·4
41·1	11·31	0·9906	27·67	436·1				Mean	436·2

380. n-*Propyl methylsuccinate.* B. p. 246·5°/763 mm.; M 216·27; n_C 1·42272, n_D 1·42486, n_F 1·43001, $n_{G'}$ 1·43381; R_C 56·00, R_D 56·25, R_F 56·84, $R_{G'}$ 57·28; $Mn_D^{20°}$ 308·16. Densities determined: $d_{4°}^{20°}$ 0·9829, $d_{4°}^{40·4°}$ 0·9654, $d_{4°}^{60·9°}$ 0·9473, $d_{4°}^{85·0°}$ 0·9252. Apparatus *D*.

23·0°	12·08	0·9802	29·24	513·1	41·9°	11·61	0·9641	27·65	514·4
26·3	12·01	0·9764	28·97	513·9	60·5	11·02	0·9476	25·79	514·3
31·3	11·85	0·9730	28·47	513·5	86·0	10·27	0·9243	23·44	514·9
								Mean	514·0

381. *Methyl crotonate.* B. p. 119°/768 mm.; M 100·11; n_C 1·42151, n_D 1·42466, n_F 1·43262, $n_{G'}$ 1·43890; R_C 26·87, R_D 27·05, R_F 27·49, $R_{G'}$ 27·83; $Mn_D^{20°}$ 142·63. Densities determined: $d_{4°}^{20°}$ 0·9458, $d_{4°}^{41·7°}$ 0·9251, $d_{4°}^{59·7°}$ 0·9058, $d_{4°}^{85·8°}$ 0·8771. Apparatus *D*.

19·0°	12·26	0·9468	28·67	244·7	60·5°	10·67	0·9050	23·83	244·4
22·9	12·20	0·9429	28·41	245·1	87·4	9·56	0·8755	20·67	244·4
41·4	11·37	0·9254	25·98	244·2				Mean	244·6

A sample of ester prepared from the silver salt and methyl iodide had b. p. 120°/772 mm., $d_4^{20°}$ 0·9457, n_C 1·42161, n_D 1·42476, n_F 1·43262, $n_{G'}$ 1·43904.

382. *Ethyl crotonate.* B. p. 136·5°/761 mm.; *M* 114·14; n_C 1·42167, n_D 1·42471, n_F 1·43228, $n_{G'}$ 1·43822; R_C 31·57, R_D 31·76, R_F 32·26, $R_{G'}$ 32·64; $Mn_D^{20°}$ 162·62. Densities determined: $d_4^{20°}$ 0·9183, $d_4^{40·8°}$ 0·8986, $d_4^{62·0°}$ 0·8772, $d_4^{87·1°}$ 0·8530. Apparatus *D*.

t.	*H.*	$d_{4^{\circ}}^{t^{\circ}}$	*γ.*	*P.*	*t.*	*H.*	$d_{4^{\circ}}^{t^{\circ}}$	*γ.*	*P.*
20·3°	12·01	0·9180	27·23	284·0	61·6°	10·47	0·8776	22·69	283·9
25·1	11·78	0·9138	26·58	283·6	87·5	9·51	0·8526	20·02	283·5
40·9	11·23	0·8985	24·92	283·8				Mean	283·8

A sample of ester prepared from silver crotonate and ethyl iodide had b. p. 136·5°/765 mm.; $d_4^{20°}$ 0·9181, n_C 1·42179, n_D 1·42481, n_F 1·43238, $n_{G'}$ 1·43837.

383. n-*Propyl crotonate.* B. p. 157·5°/768 mm.; *M* 128·17; n_C 1·42549, n_D 1·42842, n_F 1·43576, $n_{G'}$ 1·44147; R_C 36·12, R_D 36·34, R_F 36·89, $R_{G'}$ 37·31; $Mn_D^{20°}$ 183·08. Densities determined: $d_4^{20°}$ 0·9082, $d_4^{41·6°}$ 0·8892, $d_4^{61·6°}$ 0·8700, $d_4^{87·0°}$ 0·8451. Apparatus *A*.

14·1°	16·62	0·9136	28·43	324·0	61·5°	14·34	0·8701	23·36	323·9
27·8	16·05	0·9010	27·08	324·5	87·5	13·13	0·8446	20·77	323·8
41·9	15·34	0·8889	25·53	324·1				Mean	324·1

384. n-*Butyl crotonate.* B. p. 55°/4 mm.; *M* 142·19; n_C 1·42960, n_D 1·43249, n_F 1·43971, $n_{G'}$ 1·44532; R_C 40·81, R_D 41·05, R_F 41·64, $R_{G'}$ 42·10; $Mn_D^{20°}$ 203·69. Densities determined: $d_4^{20°}$ 0·8994, $d_4^{41·4°}$ 0·8811, $d_4^{61·4°}$ 0·8630, $d_4^{86·0°}$ 0·8403. Apparatus *D*.

18·5°	12·57	0·9007	27·96	363·0	61·8°	11·16	0·8626	23·72	364·0
25·3	12·38	0·8947	27·35	363·5	87·1	10·35	0·8393	21·45	364·6
41·2	11·90	0·8814	25·90	363·9				Mean	363·8

385. n-*Amyl crotonate.* B. p. 71·5°/5 mm.; *M* 156·22; n_C 1·43315, n_D 1·43600, n_F 1·44308, $n_{G'}$ 1·44848; R_C 45·46, R_D 45·71, R_F 46·36, $R_{G'}$ 46·85; $Mn_D^{20°}$ 224·33. Densities determined: $d_4^{20°}$ 0·8935, $d_4^{41·4°}$ 0·8761, $d_4^{61·6°}$ 0·8587, $d_4^{86·4°}$ 0·8370. Apparatus *A*.

18·3°	17·00	0·8949	28·49	403·3	62·0°	15·06	0·8584	24·21	403·7
27·3	16·62	0·8874	27·62	403·6	87·3	14·01	0·8363	21·94	404·3
41·1	15·94	0·8763	26·16	403·2				Mean	403·8

386. iso*Amyl crotonate.* B. p. 60°/3·5 mm.; *M* 156·22; n_C 1·43130, n_D 1·43415, n_F 1·44123, $n_{G'}$ 1·44672; R_C 45·42, R_D 45·69, R_F 46·33, $R_{G'}$ 46·83; $Mn_D^{20°}$ 224·05. Densities determined: $d_4^{20°}$ 0·8908, $d_4^{42·6°}$ 0·8712, $d_4^{61·8°}$ 0·8540, $d_4^{86·8°}$ 0·8326. Apparatus *D*.

19·7°	12·42	0·8911	27·34	400·8	62·4°	11·00	0·8535	23·19	401·6
25·0	12·26	0·8864	26·84	401·1	86·9	10·26	0·8322	21·09	402·2
41·5	11·67	0·8716	25·12	401·3				Mean	401·4

387. *Ethyl cinnamate.* B. p. 127°/6 mm.; *M* 176·21; n_C 1·55219, n_D 1·55983, n_F 1·58085; R_C 53·67, R_D 54·28, R_F 55·95; $Mn_D^{20°}$ 274·85. Densities determined: $d_4^{20°}$ 1·0494, $d_4^{42·0°}$ 1·0310, $d_4^{60·1°}$ 1·0158, $d_4^{86·2°}$ 0·9939. Apparatus *A*.

22·3°	19·18	1·0475	37·62	416·6	40·2°	18·49	1·0325	35·75	417·3
26·0	19·04	1·0444	37·24	416·8	60·6	17·68	1·0154	33·62	417·9
32·9	18·86	1·0386	36·68	417·5	87·1	16·62	0·9930	30·90	418·4
								Mean	417·4

388. n-*Propyl cinnamate.* B. p. 148°/10 mm.; *M* 190·23; n_C 1·54403, n_D 1·55123, n_F 1·57094, $n_{G'}$ 1·58908; R_C 58·41, R_D 59·05, R_F 60·79, $R_{G'}$ 62·36; $Mn_D^{20°}$ 295·12. Densities determined: $d_4^{20°}$ 1·0282, $d_4^{42·0°}$ 1·0107, $d_4^{60·6°}$ 0·9963, $d_4^{85·7°}$ 0·9756. Apparatus *A*.

21·4°	18·92	1·0270	36·38	455·0	42·1°	18·17	1·0106	34·38	455·9
24·6	18·85	1·0245	36·16	455·4	62·1	17·48	0·9951	32·57	456·7
31·0	18·66	1·0195	35·62	455·9	85·5	16·52	0·9758	30·19	457·0
								Mean	456·0

389. n-*Butyl cinnamate.* B. p. 162°/12 mm.; *M* 204·26; n_C 1·53736, n_D 1·54417, n_F 1·56283, $n_{G'}$ 1·5799 (line faint; value may be in error); R_C 63·03, R_D 63·69, R_F 65·49, $R_{G'}$ 67·12; $Mn_D^{20°}$ 315·42. Densities determined: $d_4^{20°}$ 1·0127, $d_4^{41·5°}$ 0·9961, $d_4^{60·0°}$ 0·9810, $d_4^{86·0°}$ 0·9608. Apparatus *A*.

22·5°	18·75	1·0108	35·49	493·2	61·5°	17·28	0·9798	31·70	494·7
30·9	18·50	1·0042	34·87	494·0	87·3	16·42	0·9598	29·51	496·0
41·1	18·06	0·9964	33·70	493·9				Mean	494·4

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134. *Physical Properties and Chemical Constitution. Part XVII. Acetylenic Compounds and Cyanides.*

By George H. Jeffery and Arthur I. Vogel.

New measurements are described of the parachors and refractivities (20°) of esters of but-3-yne-1-carboxylic acid and of dec-9-yne-1-carboxylic (10 : 11-undecynolic) acid. The contributions of the terminal triple bond have been computed from the general relationship

$$\mathrel{\equiv} = CH{\equiv}CR + 4H - CH_3{\cdot}CH_2R$$

employing the values for H of Part IX (*J.*, 1946, 133) and the appropriate saturated compounds to be found in previous papers of this series. The constants, which differ considerably from those previously accepted, are :

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
≡ (terminal)	40·6	1·959	1·977	2·061	2·084	−12·56

The constants similarly deduced from new experimental data for dialkyl acetylenedicarboxylates (I) and alkyl phenylpropiolates (II), in which the triple bond is non-terminal and conjugated with other groups in the molecule, are :

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
≡ in (I) (non-terminal)	46·8	3·890	3·960	4·190	4·330	−11·83
≡ in (II) (non-terminal)	45·9	5·503	5·677	6·277	6·780	−6·23

New measurements upon a series of alkyl and other cyanides are also presented and these lead, when combined with the values for alkyl groups (Part XI, this vol., p. 610), to the following constants for the C≡N group in saturated aliphatic cyanides :

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
CN	64·6	5·431	5·459	5·513	5·561	36·46

The parachor contribution of 46·6 for the carbon–carbon triple bond appears to have been deduced initially (Sugden, *J.*, 1924, **125**, 1180) from the values for acetylene and octyne, to which were later added ethyl and " *i*-butyl " phenylpropiolates (Sugden, " The Parachor and Valency ", 1930, p. 42; no details of the preparation, densities, and surface tensions seem to have been published), and it is stated (*J.*, *loc. cit.*) that this value " agress well with that found for nitriles ". Sugden does not disclose how the parachor for nitrogen was calculated, nor have figures been published supporting the constancy (or otherwise) of the parachor in different types of nitrogen-containing compounds (*e.g.*, in primary, secondary, and tertiary amines). The agreement claimed for the triple bond in acetylenic compounds and in cyanides is therefore not entirely convincing. We prefer, in the first instance to separate the two problems and to deduce independent values for the carbon–carbon triple bond in acetylenic compounds and for the C≡N grouping.

Eisenlohr (*Z. physikal. Chem.*, 1910, **75**, 604; compare von Auwers, *Ber.*, 1935, **68**, 1635) utilised the data for " propargyl alcohol, propargyl acetate, propargyl ethyl ether, oenanthilidene, caprylidene, amyl propiolacetal, hexyl propiolacetal and diacetal ", but states that the figures for the acetylene bond varied considerably and consequently the final mean value could only be regarded as approximate. Notwithstanding this admission, the constants are given to four significant figures as follows :

	R_C.	R_D.	R_F.	$R_{G'}$.
≡	2·328	2·398	2·506	2·538

In recent years a number of pure acetylenic hydrocarbons and their derivatives have been prepared (compare Campbell and O'Connor, *J. Amer. Chem. Soc.*, 1939, **61**, 2898; Campbell and Eby, *ibid.*, 1940, **62**, 180; 1941, **63**, 2384; Henne and Greenlee, *ibid.*, 1945, **67**, 484; Hennion and Banigan, *ibid.*, 1946, **68**, 1202, 1380) and their densities ($d_4^{20°}$) and refractivities ($n_D^{20°}$) determined. The refractivities R_D, calculated with Eisenlohr's constants, are not in good agreement with the observed values : attempts to obtain improved agreement have been made by Campbell and Eveslage (*ibid.*, 1945, **67**, 1851) by assigning a new set of increments for 1-, 2-, 3-, 4- and 5-acetylenes respectively and by Hennion and Banigan (*ibid.*, 1946, **68**, 1380) by employing the following atomic refractions : $C^{\equiv}$ 3·240, C^{α} 2·779, C^{β} 2·605, C^{γ} 2·436, $C^{\delta\cdots\omega}$ 2·418, and H 1·100. Apart from the fact that the values for C and H were in error (Vogel, Part IX, *J.*, 1946, 133), the procedures of the American authors are clearly empirical : a simple method is described below which gives reasonable results.

We have determined the parachors and refractivities of a number of esters of but-3-yne-1-

carboxylic acid, $CH{:}C{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$, and of dec-9-yne-1-carboxylic (10 : 11-undecynolic) acid and computed the contributions of the terminal triple bond by means of the relationship

$$\overline{\equiv} = CH{:}CR + 4H - CH_3{\cdot}CH_2R$$

utilising the values for H deduced in Part IX (*loc. cit.*) and the data for alkyl *n*-valerates (Part XIII, this vol., p. 624) and for alkyl *n*-undecylates as computed in Part XVI (preceding paper).

Our dec-9-yne-1-carboxylic acid was prepared by the action of excess of concentrated aqueous potassium hydroxide solution upon 9 : 10-dibromodecane-1-carboxylic acid (10 : 11-dibromoundecoic acid) at 150—160° in the presence of small quantities of crude sodium oleylsulphonate to reduce the attendant frothing (compare Krafft, *Ber.*, 1896, **29**, 2232; Myddelton and Barrett, *J. Amer. Chem. Soc.*, 1927, **49**, 2260). It melted at 42° and its constitution was established (*a*) by oxidation with potassium permanganate solution, whereby an almost quantitative yield of sebacic acid was obtained :

$$CH{:}C{\cdot}[CH_2]_6{\cdot}CO_2H \longrightarrow [CH_2]_8(CO_2H)_2,$$

and (*b*) by reduction of the ethyl ester with hydrogen in the presence of Adams's platinum oxide catalyst, whereupon ethyl *n*-undecylate was isolated in quantitative yield and its physical properties were in excellent agreement with those deduced in Part XVI (*loc. cit.*).

It should be noted that dec-8-yne-1-carboxylic acid (9 : 10-undecolic acid), $CH_3{\cdot}C{:}C{\cdot}[CH_2]_7{\cdot}CO_2H$, *m. p. 61°*, is formed from 9 : 10-dibromodecane-1-carboxylic acid and excess of concentrated aqueous potassium hydroxide solution *at 170°* (Harris and Smith, *J.*, 1935, 1108 : compare Krafft, *Ber.*, 1878, **11**, 1414; Welander, *ibid.*, 1895, **28**, 1445; Myddelton and Barrett, *loc. cit.*; Ashton and Smith, *J.*, 1934, 435); the reaction is under investigation.

The results for the triple-bond contributions are collected in Table I.

TABLE I.

Parachor and refractivities of the triple bond from esters, $CH{:}C{\cdot}[CH_2]_n{\cdot}CO_2R$.

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
Esters of but-3-yne-1-carboxylic acid, $CH{:}C{\cdot}[CH_2]_2{\cdot}CO_2R$.						
R = Me	40·7	1·97	1·99	2·08	2·09	−12·27
R = Et	40·2	1·98	2·00	2·08	2·12	−12·40
R = Pr^n	40·1	2·01	2·03	2·11	2·13	−12·71
R = Bu^n	39·6	2·05	2·06	2·15	2·17	−12·81
Esters of dec-9-yne-1-carboxylic acid, $CH{:}C{\cdot}[CH_2]_8{\cdot}CO_2R$.						
R = Me	41·8	1·92	1·94	2·04	2·05	−12·53
R = Et	41·1	1·87	1·88	1·94	1·98	−12·59
R = Pr^n	40·7	1·91	1·94	2·03	2·05	−12·60
Mean $\overline{\equiv}$	40·6	1·959	1·977	2·061	2·084	−12·56

It will be observed that the mean values for the parachors and refractivities differ appreciably from those previously accepted. The new constants apply only to terminal acetylenic compounds $CH{:}CR$; it is hoped in the near future to investigate compounds containing non-terminal carbon–carbon triple bonds $CR_1{:}CR_2$. Von Auwers (*Ber.*, 1935, **68**, 1635) gives for the D line values of 2·325 for terminal acetylenes and 2·573 for non-terminal acetylenes.

The results of similar measurements upon dialkyl acetylenedicarboxylates and alkyl phenylpropiolates—all of which are conjugated compounds—are presented in Tables II and III respectively : the experimental data for dialkyl succinates were taken from Part XIII (*loc. cit.*) and those for alkyl β-phenylpropionates from Part XVI (preceding paper). The high values for the refractivities were, of course, anticipated, but the higher values for the parachor (which normally does not reflect the influence of conjugation—see Part XVI on ethylenic compounds) are noteworthy.

TABLE II.

Parachor and refractivities for the triple bond in dialkyl acetylenedicarboxylates, $CO_2R{\cdot}C{:}C{\cdot}CO_2R$.

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
R = Me	46·2	3·79	3·84	4·05	4·18	−12·09
R = Et	48·4	3·94	4·03	4·25	4·39	−12·10
R = Pr^n	48·2	3·94	4·02	4·25	4·38	−11·83
R = Pr^i *	51·6	3·99	4·07	4·30	4·45	−11·72
R = Bu^n	46·3	3·86	3·91	4·14	4·30	−11·75
R = Am^n	46·9	3·97	4·05	4·29	4·42	−11·67
R = Am^i	45·0	3·84	3·91	4·16	4·31	−11·52
Mean (excluding *)	46·8	3·890	3·960	4·190	4·330	−11·83

TABLE III.

Parachor and refractivities for the triple bond in alkyl phenylpropiolates, $CPh{:}C{\cdot}CO_2R$.

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	Mn_D^{20}.
R = Et	47·0	5·48	5·68	6·27	6·77	−6·21
R = Pr^n	46·3	5·63	5·75	6·35	6·85	−6·25
R = Bu^n	44·4	5·40	5·60	6·21	6·72	−6·24
Mean	45·9	5·503	5·677	6·277	6·780	−6·23

Determination of the parachors and refractivities of seven aliphatic cyanides, allyl cyanide, trimethylene dicyanide, phenyl cyanide, and benzyl cyanide have also been made. The CN contributions for the aliphatic nitriles have been computed with the aid of the constants for the alkyl groups given in Part XI (this vol., p. 610), for trimethylene dicyanide using the CH_2 values from Part IX (*J.*, 1946, 133), phenyl cyanide from phenyl (Part XV, this vol., p. 654), and benzyl cyanide from $C_6H_5{\cdot}CH_3 - H$ (Part X, this vol., p. 607, and Part IX, *loc. cit.*). The preferred values for CN are derived from the saturated aliphatic nitriles. The results are given in Table IV. Measurements of the densities and refractivities at 0°, 15°, and 30° of a long series

TABLE IV.

Parachor and refractivities for the CN *group in cyanides.*

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
MeCN	66·2	5·40	5·44	5·49	5·54	37·05
EtCN	65·5	5·42	5·45	5·51	5·56	36·51
Pr^{n}CN	64·9	5·45	5·46	5·52	5·57	36·41
Bu^{n}CN	64·9	5·40	5·42	5·47	5·51	36·58
Am^{n}CN	63·0	5·44	5·47	5·51	5·56	36·23
Am^{i}CN	63·9	5·49	5·52	5·58	5·63	36·30
$C_6H_{13}^n{\cdot}CN$	—	5·42	5·45	5·51	5·56	36·12
Mean C≡N	64·6	5·431	5·459	5·513	5·561	36·46
$[CH_2]_3(CN)_2$	65·8	5·31	5·33	5·36	5·42	36·39
$C_2H_5{\cdot}CN$	63·5	5·13	5·15	5·18	5·21	36·72
$C_6H_5{\cdot}CN$	69·0	6·07	6·12	6·23	6·32	35·70
$C_6H_5{\cdot}CH_2{\cdot}CN$	64·4	5·14	5·17	5·19	5·19	37·93

of carefully purified aliphatic nitriles have been made by Merckx, Verhulst, and Bruylants (*Bull. Soc. chim. Belg.*, **1933**, **42**, 177): although the methods of preparation, in many cases, differed from our own, the interpolated values for $d_{4°}^{20°}$ and $n_D^{20°}$ are in good agreement.

We have employed the experimental data given by Henne and Greenlee (*J. Amer. Chem. Soc.*, 1945, **67**, 484) and by Hennion and Banigan (*ibid.*, 1946, **68**, 1380) for $d_{4°}^{20°}$, $n_D^{20°}$, and R_D for the calculation of the refractivity for the triple bond, utilising our own values for H and for saturated aliphatic hydrocarbons (Part IX, *loc. cit.*). The results for terminal acetylenes (which alone are strictly comparable with our own data for terminal acetylenic compounds) are collected in Table V.

TABLE V.

Values for the triple bond in hydrocarbons and alcohols with terminal acetylenic groups.

Compound.	≡.	R_D, obs.	R_D, calc. (Authors.)	R_D, calc. (H. and B.)
Pent-1-yne	1·95	23·12	23·16	23·10
Hex-1-yne	1·95	27·77	27·79	27·74
Hept-1-yne	1·95	32·44	32·43	32·34
5-Methylhex-1-yne	1·98	32·47	32·43	32·34
Oct-1-yne	2·00	37·06	37·08	36·95
Hepta-1 : 6-diyne	1·96	30·30	30·28	29·92 *
Nona-1 : 8-diyne	1·94	39·52	39·58	39·36 *
Prop-1-yne-3-ol	1·91	15·34	15·36	15·18 *
But-1-yne-4-ol	1·96	19·90	20·01	19·99 *
3 : 3-Dimethylprop-1-yne-3-ol	2·01	24·77	24·65	24·79 *

In deducing the figures for the triple bond we have employed our own (unpublished) data for the corresponding saturated alcohols. The values for the triple bond agree well with those deduced from our own measurements. The calculated values for R_D employing our own figures for C, H, OH (2·543), and ≡ (in CH:CR) are given in col. 4. Hennion and Banigan's figures are in col. 5; those marked with an asterisk have been computed by us with their constants and Eisenlohr's values for OH.

The results for acetylenic hydrocarbons with non-terminal acetylene groups are given in Table VI. The mean value of the refractivity of the triple bond for the D line at 20° is 2·35 with a variation from the mean of ± 0·10. It would therefore appear that the refractivity of the triple bond in these compounds is greater than that in compounds with the terminal ⋮CH group. The calculated refractivities derived with the aid of the authors' C and H constants and the above non-terminal triple bond value are reasonably satisfactory and render the highly empirical procedures of Campbell and Eveslage (*J. Amer. Chem. Soc.*, 1945, **67**, 1851) and of Hennion and Banigan (*loc. cit.*) superfluous.

TABLE VI.

Values for the triple bond in hydrocarbons with non-terminal acetylenic groups.

Hydrocarbon.	F.	R_D, obs.	R_D, calc. (Authors.)	R_D, calc. (H. and B.)
Pent-2-yne	2·28	23·44	23·53	23·44
Hex-3-yne	2·39	28·20	28·18	28·25
Oct-2-yne	2·25	37·31	37·47	37·32
Oct-3-yne	2·40	37·46	37·47	37·50
Oct-4-yne	2·45	37·51	37·47	37·52
Non-3-yne	2·35	42·09	42·12	42·12
Dec-5-yne	2·36	46·75	46·76	46·75
Undec-5-yne	2·27	51·31	51·41	51·37
Nona-2 : 7-diyne	2·42	40·57	40·36	39·88
Mean	2·35			

EXPERIMENTAL.

Esters of But-3-yne-1-carboxylic Acid.—But-3-yne-1-carboxylic acid. Allyl bromide, b. p. 71—72° (XVI, **357**), was converted into 1 : 2 : 3-tribromopropane, b. p. 92—93°/10 mm. (*Org. Synth.*, Coll. Vol. I, 1941, 521), and then condensed with ethyl sodioacetoacetate (Gardner and Perkin, *J.*, 1907, **91**, 848). The pure ester, $CH_2{:}CBr{\cdot}CH_2{\cdot}CH(COMe){\cdot}CO_2Et$, b. p. 114—115°/10 mm. (Gardner and Perkin, *loc. cit.*, give b. p. 120—121°/8 mm.), was isolated by fractionation from a Scorah flask and was treated with methyl-alcoholic potassium hydroxide (Perkin and Simonsen, *J.*, 1907, **91**, 822) to give but-3-yne-1-carboxylic acid, m. p. 54°; recrystallisation from light petroleum (b. p. 40—60°) raised the m. p. to 56—57°. The yield of acid from 46 g. of sodium, 600 ml. of absolute ethyl alcohol, 260 g. of ethyl acetoacetate, and 290 g. of tribromopropane was 21 g. A mixture of 10 g. of the acid, 80 g. of absolute methyl alcohol, and 6 g. of concentrated sulphuric acid was kept at room temperature for 1 week, poured into water, and the separated oil extracted with ether, dried, and distilled. This gave 9 g. of the *methyl* ester, b. p. 146·5°/754 mm. (Found : C, 64·0; H, 7·3. $C_5H_8O_2$ requires C, 64·3; H, 7·2%).

Ethyl ester. (1) By the above method, but with 90 g. of absolute ethyl alcohol, 9 g. of this ester were obtained; b. p. 159°/763 mm. (Perkin and Simonsen, *loc. cit.*, give b. p. 160—161°).

(2) A mixture of 10 g. of the acid, 9 ml. of absolute ethyl alcohol, 1 ml. of concentrated sulphuric acid, and 18 ml. of sodium-dried A.R. benzene was refluxed for 12 hours. The resulting dark liquid, after being poured into water and worked up in the usual manner, afforded 7 g. of a liquid ester, b. p. 195°/763 mm., $d_4^{20°}$ 1·0049, $n_D^{20°}$ 1·4241. It was evidently not the desired ester and was not further investigated.

n-*Propyl ester.* A mixture of 10 g. of the acid, 120 g. of pure *n*-propyl alcohol, and 8 g. of concentrated sulphuric acid, kept at room temperature for 21 days and worked up in the usual manner, gave 6 g. of the n-*propyl* ester, b. p. 174·5—175·5°/763 mm. (Found : C, 68·4; H, 8·7. $C_8H_{12}O_2$ requires C, 68·5; H, 8·6%).

n-*Butyl ester.* To a cold solution of 10 g. of concentrated sulphuric acid in 180 ml. of pure *n*-butyl alcohol were added 12·5 g. of the acetylenic acid, the mixture was kept at room temperature for 24 days, and then poured into excess of water. The upper, organic layer was removed, washed successively with water, saturated sodium hydrogen carbonate solution until effervescence ceased, and water, dried ($CaCl_2$), and fractionated. *n*-Butyl alcohol passed over first and when the volume was about 25 ml. much solid separated (presumably the addition compound $CaCl_2,x\text{Bu}^n\text{OH}$). When this was cold, anhydrous ether was added, the solid filtered off, the ether removed, and the residue distilled; 8 g. of the n-*butyl* ester (a very pale yellow liquid) were collected at 193·5—194·5°/759 mm. Redistillation gave a perfectly colourless liquid, b. p. 71°/6 mm. (Found : C, 69·8; H, 9·1. $C_9H_{14}O_2$ requires C, 70·1; H, 9·2%).

Esters of Dec-9-yne-1-carboxylic Acid.—Dec-9-yne-1-carboxylic acid. Undecylenic acid was purified through the methyl ester (preceding paper) and had a setting point of 23·5°; practically identical results were obtained with the redistilled acid, b. p. 152—154°/6 mm., s. p. 22·6—22·8°. In a 1500-ml. three-necked flask, equipped with a double-surface condenser, a mercury-sealed mechanical stirrer, and a dropping-funnel, was placed a solution of 108 g. of purified undecylenic acid in 285 ml. of dry A.R. carbon tetrachloride. The solution was cooled in a bath of ice and salt and 96 g. of dry A.R. bromine were added during 1 hour. The product was allowed to attain room temperature, the solvent distilled off from a water-bath, and the residue transferred to a basin; after standing in the air for several days (or keeping in a vacuum desiccator over silica gel), it solidified completely. The yield of 9 : 10-dibromodecane-1-carboxylic acid was quantitative.

The solid dibromo-acid was mixed with a solution of 263 g. of potassium hydroxide in 158 ml. of water in a 2-l. round-bottomed flask equipped with a double-surface condenser, and the whole heated

in a bath at 150—160° for 8 hours; foaming was reduced by addition of small quantities of crude sodium oleylsulphonate (" pentrone-T ") from time to time. After the product had stood overnight, 1·5 l. of water were added, and the mixture was shaken until the solid had dissolved, acidified with dilute sulphuric acid to Congo-red, and set aside for 12 hours, whereupon a cake of acid separated on the surface. This was extracted with four 250-ml. portions of ether, the ether removed, and the residue distilled with a free flame. Two fractions were collected: (*a*) b. p. 177—182°/15 mm., 52 g., solidifying completely on cooling to a solid, m. p. 38—41°, and (*b*) b. p. 182—200°/15 mm., 15 g., solidifying on cooling to a somewhat sticky solid. Recrystallisation of (*a*) from A.R. light petroleum (b. p. 60—80°) yielded a first crop of 31 g. of acid, m. p. 42°; the filtrate was allowed to evaporate spontaneously, and the resulting sticky solid, after being spread on porous porcelain and recrystallised, gave a further 2 g. of acid, m. p. 42°. Fraction (*b*), after similar treatment afforded 3 g. of acid, m. p. 42°. Further recrystallisation did not alter the m. p.

In another experiment a mixture of 120 g. of the dibromo-acid and a solution of 140 g. of potassium hydroxide in 90 ml. of water, contained in a 2-l. flask fitted with a reflux condenser, was heated in an oil-bath at 160° for 30 minutes; much foaming occurred. Upon working up as above, there were obtained: (*a*) 25 g., b. p. 177—180°/17 mm.; this solidified immediately on cooling (m. p. 40—42°) and after recrystallisation from light petroleum (b. p. 40—60°) had m. p. 42° (16 g.); (*b*) 19 g., b. p 180—210°/17 mm., which set to a soft sticky mass on cooling and yielded only 1 g. of the acid, m. p. 42° (Found: equiv., 184. Calc. for $C_{11}H_{18}O_2$: equiv., 182).

Oxidation of the acetylenic acid of m. p. 42°. 2·00 G. of the acid were dissolved in 50 ml. of water containing 0·585 g. of A.R. anhydrous sodium carbonate, the solution was kept saturated with carbon dioxide, and 0·1N-potassium permanganate solution was added slowly and with constant stirring until a slight excess was present after standing for 30 minutes (compare Perkin and Simonsen, *J.*, 1907, **91**, 828): 1500 ml. were required and the addition occupied 3 hours. The solution was decolorised with sulphur dioxide and kept for 24 hours at room temperature. The acid was filtered off through a weighed Gooch crucible and dried to constant weight; its m. p. was 133°, unaffected by recrystallisation from acetone, and unaltered by admixture with pure sebacic acid, m. p. 133—134°. The yield of sebacic acid was 1·45 g.; to this must be added the dissolved acid contained in 1550 ml. of solution. There can therefore be little doubt that the acid, m. p. 42°, is dec-9-yne-1-carboxylic acid.

Methyl ester. A mixture of 13 g. of the acetylenic acid, 80 g. of absolute methyl alcohol, and 10 g. of concentrated sulphuric acid was kept at room temperature for 14 days, poured into excess of water, and extracted with ether. The ethereal extract was washed with saturated sodium hydrogen carbonate solution and water, dried ($MgSO_4$), and the solvent removed. Distillation gave 12 g. of the pure *methyl* ester, b. p. 121°/5 mm. (Found: C, 72·9; H, 10·1. $C_{12}H_{20}O_2$ requires C, 73·4; H, 10·0%).

Ethyl ester. (1) A mixture of 15 g. of the acid, 9 g. of absolute ethyl alcohol, 1 ml. of concentrated sulphuric acid, and 25 ml. of sodium-dried A.R. benzene was refluxed for 38 hours and yielded, after being worked up in the usual manner, 12·5 g. of ester, b. p. 134·5°/6·5 mm.

(2) A mixture of 10 g. of the acid, 50 g. of absolute ethyl alcohol, and 6 g. of concentrated sulphuric acid was kept at room temperature for 8 days and afforded, as for the methyl ester, 10 g. of ethyl ester of b. p. 142°/13 mm.

n-*Propyl ester.* (1) A mixture of 10 g. of the acid, 80 g. of pure anhydrous *n*-propyl alcohol, and 6 g. of concentrated sulphuric acid was kept at room temperature for 20 days, poured into excess of water, and extracted with ether. The extract was purified as above, and the ether and the excess of alcohol were removed at atmospheric pressure. Further distillation gave 9 g. of the n-*propyl* ester, b. p. 142°/6 mm. (Found: C, 75·0; H, 10·7. $C_{14}H_{24}O_2$ requires C, 75·0; H, 10·8%).

(2) A mixture of 12 g. of the acid, 10 g. of pure *n*-propyl alcohol, 3 g. of concentrated sulphuric acid, and 25 ml. of sodium-dried A.R. benzene was refluxed for 20 hours. After working up as usual, 12 g. of ester, b. p. 161—162°/13 mm., 138°/5 mm., were obtained; this had $d_4^{20°}$ 0·9051, $n_D^{20°}$ 1·4457, R_D 66·06 (*M*, 224·33), and was evidently not the desired product.

Reduction of ethyl ester: ethyl n-*undecylate.* 19·5 G. of the acetylenic ester were mixed with 25 ml. of absolute ethyl alcohol and reduced with hydrogen at atmospheric pressure in the presence of 0·3 g. of Adams's platinum oxide catalyst. 4470 Ml. of hydrogen were absorbed during 4·5 hours and no further absorption occurred during 5 hours; the theoretical absorption (765 mm. and 20°) is 4505 ml. plus 60 ml. for the reduction of the platinum oxide catalyst. The platinum was filtered off, the alcohol removed at atmospheric pressure and the ester distilled, whereby 18 g., b. p. 115·5°/5 mm., were obtained. The ester was slightly turbid; the turbidity was removed by dissolving in ether, washing with sodium hydrogen carbonate solution (there was no apparent reaction) and water, drying, and distilling: b. p. 118°/7 mm. The physical properties agreed with those calculated from 0·5(ethyl *n*-decoate + ethyl *n*-dodecoate) and from ethyl *n*-decoate + CH_2 (Part XIII, this vol., p. 624; compare preceding paper).

Esters of Acetylenedicarboxylic Acid.—Acetylenedicarboxylic acid, prepared from pure fumaric acid as described in *Org. Synth.*, 1938, **18**, 17, 3, had m. p. 177—178° (*Org. Synth., loc. cit.*, gives m. p. 175—176°; Moureu and Bongrand, *Ann. Chim.*, 1920, **14**, 9, give m. p. 178·5—179°).

Dimethyl ester. (1) The following modification of Moureu and Bongrand's method (*loc. cit.*) was employed. In a 1-l. three-necked flask, provided with a thermometer, mechanical stirrer, and reflux condenser protected by a calcium chloride tube, was placed a cold mixture of 80 g. of pure anhydrous methyl alcohol and 40 g. of concentrated sulphuric acid: 20 g. of acetylenedicarboxylic acid were added, the mixture kept at room temperature for 66 hours and then, with stirring, at 50° for 58 hours. The mixture was poured into 120 ml. of saturated salt solution and extracted with five 80-ml. portions of ether: the combined extracts were washed with water, saturated sodium hydrogen carbonate solution (until colourless), and water, dried (Na_2SO_4), and the solvent removed on a water-bath. The residue upon distillation gave 13·7 g. of ester, b. p. 76·5°/3 mm.

(2) A mixture of 20 g. of acid, 16 g. of absolute methyl alcohol, 40 ml. of sodium-dried A.R. benzene, and 7 g. of concentrated sulphuric acid was refluxed for 5 hours, poured into 120 ml. of saturated salt solution, the benzene layer separated, and the aqueous phase extracted with three 150-ml. portions of ether. The combined extracts were worked up as in (1), the ether was removed on a water-bath and the

benzene under reduced pressure (water-pump), and the residue distilled (oil-pump); 15·5 g. of ester, b. p. 78·5°/4 mm., were obtained.

Diethyl ester. A mixture of 20 g. of the acid, 23 g. of absolute ethyl alcohol, 60 ml. of dry benzene, and 4 ml. of concentrated sulphuric acid was refluxed for 12 hours and yielded, as for the methyl ester, 20·5 g. of the ester, b. p. 85·5°/2·5 mm.

Di-n-*propyl ester.* A mixture of 20 g. of the acid, 30 g. of anhydrous *n*-propyl alcohol, 5 ml. of concentrated sulphuric acid, and 80 ml. of dry benzene was refluxed for 12·5 hours and yielded 24·9 g. of the *di*-n-*propyl* ester, b. p. 116°/5 mm. (Found: C, 60·5; H, 7·1. $C_{10}H_{14}O_4$ requires C, 60·6; H, 7·1%).

Diisopropyl ester. The same procedure (same quantities, 10 hours' refluxing) afforded 21·6 g. of ester, b. p. 96°/3 mm.

Di-n-*butyl ester.* A mixture of 15 g. of acid, 27 g. of absolute *n*-butyl alcohol, 70 ml. of dry benzene, and 5 ml. of concentrated sulphuric acid was refluxed for 19 hours and yielded, after two distillations, 15·5 g. of the n-*butyl* ester, b. p. 139°/5 mm. (Found: C, 63·6; H, 8·2. $C_{12}H_{18}O_4$ requires C, 63·7; H, 8·0%).

Di-n-*amyl ester.* A mixture of 20 g. of acid, 60 g. of *n*-amyl alcohol (Sharples, b. p. 136·5—137·5°/765 mm.), 150 ml. of dry benzene, and 8 ml. of concentrated sulphuric acid was refluxed for 18 hours and yielded, after two distillations, 26·0 g. of the n-*amyl* ester, b. p. 143°/1·5 mm. (Found: C, 66·0; H, 8·9. $C_{14}H_{26}O_4$ requires C, 66·1; H, 8·7%).

Diisoamyl ester. *iso*Butylcarbinol (Sharples, b. p. 129—130°/763 mm.), under exactly the same conditions (but 24 hours' refluxing), gave 28·5 g. of the iso*amyl* ester, b. p. 133°/2·5 mm. (Found: C, 66·1; H, 8·7. $C_{14}H_{26}O_4$ requires C, 66·1; H, 8·7%).

Esters of Phenylpropiolic Acid.—Phenylpropiolic acid, prepared according to *Org. Synth.*, 1932, **12**, 60, and recrystallised from A.R. carbon tetrachloride, had m. p. 134—135°.

Ethyl ester. A mixture of 120 g. of absolute ethyl alcohol and 9 g. of concentrated sulphuric acid was treated with 20 g. of phenylpropiolic acid, kept at room temperature for 7 days, poured into water, and the separated oil extracted with ether. The extract was washed successively with water, saturated sodium hydrogen carbonate solution, and water, dried, and the solvent removed. Distillation gave 18 g. of the ester, b. p. 124°/6 mm. Attempts to prepare the ester from silver phenylpropiolate and ethyl iodide in benzene solution were unsuccessful.

n-*Propyl ester.* A solution of 10 g. of concentrated sulphuric acid in 156 g. of absolute *n*-propyl alcohol was treated with 20 g. of phenylpropiolic acid and kept for 14 days at room temperature. After the same procedure as for the ethyl ester, the ether and excess of *n*-propyl alcohol were removed by heating in a bath to 130—140°. The residue, after two distillations, gave 17 g. of the n-*propyl* ester, b. p. 143°/7 mm. (Found: C, 76·4; H, 6·4. $C_{12}H_{12}O_4$ requires C, 76·6; H, 6·4%).

n-*Butyl ester.* To a cold solution of 13 g. of concentrated sulphuric acid in 195 g. of absolute *n*-butyl alcohol were added 20 g. of phenylpropiolic acid, and the mixture kept for 28 days at room temperature. This yielded, when worked up as for the *n*-propyl ester, 10 g. of the n-*butyl* ester, b. p. 149°/5 mm. (Found: C, 76·9; H, 7·1. $C_{13}H_{14}O_2$ requires C, 77·2; H, 7·0%).

Cyanides.—Methyl cyanide. 80 G. of pure acetamide (b. p. 219°/762 mm., m. p. 80—81°) were heated with 140 g. of phosphoric oxide and yielded, in the usual manner, 38 g. of methyl cyanide, b. p. 81°/757 mm.

Ethyl cyanide. The following procedure is based upon that given by Adams and Marvel (" Organic Chemical Reagents ", 1921, III, 47; University of Illinois, 1921) (compare Walden, *Ber.*, 1907, **40**, 3215). In a 500-ml. three-necked flask, mounted on a wire gauze and equipped with a dropping funnel, mechanical stirrer, and wide-bored " knee-tube " attached to a double-surface condenser set for downward distillation, was placed a solution of 118 g. of sodium cyanide in 150 ml. of water. 192 G. of commercial ethyl sulphate were added to the boiling mixture at about the same rate as the liquid distilled; the addition was complete in 1 hour, 50 ml. of water were added, and the residual ethyl cyanide boiled out. The upper layer in the distillate was separated; the aqueous phase was saturated with calcium chloride, cooled in ice, and the small quantity of cyanide removed. To destroy the *iso*cyanide present, the product was shaken twice for 5 minutes with 5-ml. portions of concentrated hydrochloric acid; it was then washed with saturated potassium carbonate solution, shaken with calcium chloride solution, and dried (Na_2SO_4). The crude ethyl cyanide (62 g.) was fractionated and yielded 21 g., b. p. 96·5—98·5°/760 mm.; the low b. p. fraction (*ca.* 20 g.) was again dried ($NaSO_4$) and redistilled to give 10 g., b. p. 55—96° (a liquid with a pungent odour, which was not further investigated), and 10 g., b. p. 96—98°. Upon redistillation, the ethyl cyanide boiled constantly at 97·5°/765 mm. Attempts to prepare ethyl cyanide from aqueous methyl-alcoholic sodium cyanide and ethyl bromide gave unsatisfactory results.

n-*Propyl cyanide.* To a solution of 60 g. of sodium cyanide in 80 ml. of water contained in a 1-l. round-bottomed flask was added a solution of 124 g. of *n*-propyl bromide in 260 ml. of methyl alcohol. The mixture was refluxed for 39 hours, the liquid decanted into another flask, and the residual solid washed with 50 ml. of methyl alcohol. The methyl alcohol was removed by careful fractionation through a 3-section, Pyrex Young and Thomas column from a water-bath; further fractionation from an air-bath gave two fractions, b. p. 70—90° and 90—102°. Each was saturated with calcium chloride, the upper layers removed, combined, and shaken successively with a few ml. of concentrated hydrochloric acid (to remove *iso*cyanide), sodium hydrogen carbonate solution, calcium chloride solution, and dried (Na_2SO_4). Fractionation of the dry crude product (25 g.) afforded 19 g. of *n*-propyl cyanide, b. p. 117·8—118·8°/758 mm. Redistillation gave the pure compound, b. p. 118°/757 mm.

n-*Butyl cyanide.* The following modification of Adams and Marvel's method (*J. Amer. Chem. Soc.*, 1920, **42**, 311) was employed. To a warm solution (steam-bath) of 195 g. of sodium cyanide in 250 ml. of water contained in a 3-l. round-bottomed flask was added a solution of 450 g. of *n*-butyl bromide in 575 ml. of methyl alcohol. The mixture was refluxed for 30 hours and, when cold, filtered through a sintered-glass funnel, and the solid washed with 200 ml. of methyl alcohol. The combined filtrate and washings were distilled from a 2-l. flask and three-section, Young and Thomas column mounted on a water-bath; the temperature of the vapours did not rise above 68—69°. One litre of water was added

to the residue in the flask, the latter fitted with a " knee-tube " attached to a downward condenser, and the liquid distilled until oil ceased to pass over. The water in the distillate was discarded, and the crude cyanide (200 g.) washed twice with half its volume of concentrated hydrochloric acid (to remove *iso*cyanides), then with saturated sodium hydrogen carbonate solution, and dried with ($MgSO_4$). Distillation gave the pure cyanide, b. p. 141°/764 mm.

n-*Amyl cyanide.* A solution of 30 g. of sodium cyanide in 40 ml. of water was mixed with a solution of 100 g. of *n*-amyl iodide in 125 ml. of methyl alcohol, and the whole refluxed for 30 hours: no solid separated. The crude cyanide, isolated as for *n*-butyl cyanide, weighed 39 g. It boiled constantly at 162°/777 mm.

iso*Amyl cyanide.* This was prepared by refluxing a mixture of 30 g. of sodium cyanide in 40 ml. of water and 77 g. of *iso*amyl bromide (*ex* Sharples's synthetic alcohol) in 150 ml. of methyl alcohol for 27 hours. The yield, b. p. 153·5°/756 mm., was 25 g.

n-*Hexyl cyanide.* This was prepared by refluxing a mixture of 30 g. of sodium cyanide in 40 ml. of water and a solution of 82 g. of *n*-hexyl bromide in 150 ml. of methyl alcohol for 21 hours. The cyanide was isolated as detailed for *n*-butyl cyanide except that it was preferable to separate the crude cyanide layer from the diluted reaction product after the methyl alcohol had been removed by careful fractionation: steam distillation was rather slow. The yield of *n*-hexyl cyanide, b. p. 182—182·5°/757 mm., was 40 g.

Allyl cyanide. A large-scale preparation, b. p. 116—121°/754 mm. (preceding paper), was carefully fractionated, and a large middle fraction, b. p. 118·5°/753 mm., was employed in the physical measurements.

Trimethylene dicyanide. This was prepared from the dibromide, b. p. 164—165·5°/759 mm., as detailed in *Org. Synth.*, Coll. Vol. I, 1941, 536, and boiled at 140°/8 mm.

Phenyl cyanide. 45 G. of benzamide, m. p. 128°, were mixed with 75 g. of phosphoric oxide in a 250-ml. Claisen flask, arranged for distillation under diminished pressure (*ca.* 100 mm.). The flask was heated with a free flame and the cyanide (32 g.) passed over at 126—130°/100 mm. The product was washed with potassium carbonate solution, dried, and distilled: the phenyl cyanide boiled constantly at 189°/758 mm.

Benzyl cyanide. This was prepared by refluxing a mixture of a solution of 30 g. of sodium cyanide in 40 ml. of water and a solution of 63 g. of redistilled benzyl chloride in 125 ml. of methyl alcohol for 30 hours. The cyanide was isolated as detailed for *n*-butyl cyanide except that it was necessary to separate the benzyl cyanide from the steam distillate by ether extraction. The yield was 40 g., b. p. 108·5°/15 mm.

Physical Measurements.—**390.** *Methyl but-3-yne-1-carboxylate.* B. p. 146·5°/754 mm.; *M* 112·12; n_C 1·42670, n_D 1·42917, n_F 1·43526, $n_{G'}$ 1·43979; R_C 29·17, R_D 29·32, R_F 29·69, $R_{G'}$ 29·95; $Mn_D^{20°}$ 160·24. Densities determined: $d_{4°}^{20°}$ 0·9861, $d_{4°}^{41·8°}$ 0·9641, $d_{4°}^{61·0°}$ 0·9450, $d_{4°}^{86·1°}$ 0·9186. Apparatus *D*.

(These headings apply to corresponding columns of all subsequent tables.)

t.	*H.*	$d_{4°}^{t°}$.	γ.	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	γ.	*P.*
15·3°	13·68	0·9908	33·47	272·2	63·3°	11·82	0·9427	27·52	272·4
19·4	13·59	0·9867	33·12	272·6	86·2	10·85	0·9185	24·61	271·9
42·6	12·61	0·9633	30·00	272·4				Mean	272·3

391. *Ethyl but-3-yne-1-carboxylate.* B. p. 159°/763 mm.; *M* 126·15; n_C 1·42563, n_D 1·42803, n_F 1·43403, $n_{G'}$ 1·43849; R_C 33·88, R_D 34·05, R_F 34·46, $R_{G'}$ 34·78; $Mn_D^{20°}$ 180·14. Densities determined: $d_{4°}^{20°}$ 0·9532, $d_{4°}^{41·0°}$ 0·9328, $d_{4°}^{61·0°}$ 0·9126, $d_{4°}^{85·0°}$ 0·8879. Apparatus *A*.

17·4°	17·15	0·9558	30·69	310·7	61·4°	14·99	0·9122	25·60	311·1
21·4	17·04	0·9518	30·37	311·1	87·8	13·69	0·8851	22·69	311·1
41·4	15·97	0·9324	27·88	310·9				Mean	311·0

[Perkin and Simonsen, *loc. cit.*, give b. p. 160—161°/765 mm., $d_{4°}^{16·7°}$ 0·95585, $n_C^{16·7°}$ 1·42673, $n_F^{16·7°}$ 1·43516, $n_{G'}^{16·7°}$ 1·44001.]*

392. n-*Propyl but-3-yne-1-carboxylate.* B. p. 174·5—175·5°/763 mm.; *M* 140·18; n_C 1·42714, n_D 1·42952, n_G 1·43542, $n_{G'}$ 1·43975; R_C 38·50, R_D 38·69, R_F 39·15, $R_{G'}$ 39·49; $Mn_D^{20°}$ 200·39. Densities determined: $d_{4°}^{20°}$ 0·9351, $d_{4°}^{41·2°}$ 0·9141, $d_{4°}^{60·1°}$ 0·8958, $d_{4°}^{86·3°}$ 0·8704. Apparatus *D*.

14·1°	13·13	0·9409	30·51	350·1	40·4°	12·19	0·9149	27·54	351·0
18·4	13·01	0·9367	30·10	350·5	61·3	11·44	0·8946	25·27	351·3
22·3	12·89	0·9328	29·69	350·8	85·9	10·57	0·8707	22·73	351·5
								Mean	350·9

393. n-*Butyl but-3-yne-1-carboxylate.* B. p. 193·5—194·5°/759 mm. and 71°/6 mm.; *M* 154·20; n_C 1·42980, n_D 1·43219, n_F 1·43807, $n_{G'}$ 1·44244; R_C 43·10, R_D 43·31, R_F 43·82, $R_{G'}$ 44·19; $Mn_D^{20°}$ 220·85. Densities determined: $d_D^{20°}$ 0·9239, $d_{4°}^{44·5°}$ 0·9015, $d_{4°}^{61·7°}$ 0·8858, $d_{4°}^{85·1°}$ 0·8643. Apparatus *D*.

22·1°	12·86	0·9220	29·28	389·1	63·0°	11·48	0·8846	25·08	390·1
27·3	12·67	0·9172	28·70	389·1	85·6	10·72	0·8638	22·87	390·4
41·3	12·15	0·9054	27·17	388·8				Mean	389·5

394. *Methyl dec-9-yne-1-carboxylate.* B. p. 121°/5 mm.; *M* 196·28; n_C 1·44403, n_D 1·44646, n_F 1·45242, $n_{G'}$ 1·45688; R_C 56·81, R_D 57·09, R_F 57·75, $R_{G'}$ 58·24; $Mn_D^{20°}$ 283·92. Densities determined: $d_{4°}^{20°}$ 0·9177, $d_{4°}^{40·0°}$ 0·9020, $d_{4°}^{62·6°}$ 0·8845, $d_{4°}^{84·3°}$ 0·8665. Apparatus *D*.

t.	*H.*	$d_{4^\circ}^{t^\circ}$.	*γ.*	*P.*	*t.*	*H.*	$d_{4^\circ}^{t^\circ}$.	*γ.*	*P.*
17·0°	14·72	0·9201	33·45	513·0	61·5°	13·16	0·8849	28·76	513·7
20·0	14·60	0·9177	33·09	513·0	86·7	12·27	0·8646	26·20	513·6
41·9	13·85	0·9003	30·79	513·6				Mean	513·4

395. *Ethyl dec-9-yne-1-carboxylate.* B. p. 134·5°/6·5 mm.; *M* 210·31; n_C 1·44232, n_D 1·44475, n_F 1·45061, $n_{G'}$ 1·45505; R_C 61·42, R_D 61·72, R_F 62·41, $R_{G'}$ 62·95; $Mn_D^{20^\circ}$ 303·86. Densities determined: $d_{4^\circ}^{20^\circ}$ 0·9066, $d_{4^\circ}^{41\cdot6^\circ}$ 0·8897, $d_{4^\circ}^{61\cdot9^\circ}$ 0·8734, $d_{4^\circ}^{87\cdot1^\circ}$ 0·8534. Apparatus *D*.

12·3°	14·56	0·9123	32·80	551·7	61·9°	12·77	0·8734	27·54	551·6
20·5	14·28	0·9062	31·96	551·8	88·6	11·89	0·8522	25·02	552·0
42·2	13·49	0·8892	29·62	551·8				Mean	551·8

The ester prepared by the cold esterification process had b. p. 142°/13 mm., $d_{4^\circ}^{20^\circ}$ 0·9069, $n_{4^\circ}^{20^\circ}$ 1·44480.

396. n-*Propyl dec-9-yne-1-carboxylate.* B. p. 142°/6 mm.; *M* 224·33; n_C 1·44343, n_D 1·44586, n_F 1·45175, $n_{G'}$ 1·45618; R_C 66·09, R_D 66·41, R_F 67·17, $R_{G'}$ 67·74; $Mn_D^{20^\circ}$ 324·36. Densities determined: $d_{4^\circ}^{20^\circ}$ 0·9006, $d_{4^\circ}^{40\cdot8^\circ}$ 0·8849, $d_{4^\circ}^{61\cdot9^\circ}$ 0·8690, $d_{4^\circ}^{85\cdot5^\circ}$ 0·8509. Apparatus *D*.

19·2°	14·30	0·9012	31·83	591·2	41·7°	13·60	0·8840	29·69	591·0
20·3	14·25	0·9004	31·69	591·1	61·0	12·93	0·8697	27·77	592·1
29·5	13·98	0·8934	30·84	591·7	87·2	12·08	0·8496	25·35	592·4
								Mean	591·6

397. *Ethyl* n-*undecylate.* B. p. 118°/7 mm.; *M* 214·34; n_C 1·42630, n_D 1·42847, n_F 1·43376, $n_{G'}$ 1·43760; R_C 63·65, R_D 63·94, R_F 64·63, $R_{G'}$ 65·12; $Mn_D^{20^\circ}$ 306·18. Densities determined: $d_{4^\circ}^{20^\circ}$ 0·8633, $d_{4^\circ}^{41\cdot2^\circ}$ 0·8476, $d_{4^\circ}^{61\cdot7^\circ}$ 0·8319, $d_{4^\circ}^{86\cdot3^\circ}$ 0·8123. Apparatus *A*.

16·8°	17·65	0·8658	28·61	572·6	61·3°	15·75	0·8322	24·54	573·3
20·7	17·48	0·8628	28·24	572·7	86·4	14·72	0·8122	22·39	574·0
42·4	16·68	0·8467	26·45	573·9				Mean	573·3

398. *Dimethyl acetylenedicarboxylate.* B. p. 76·5°/3 mm.; *M* 142·11; n_C 1·44389, n_D 1·44681, n_F 1·45483, $n_{G'}$ 1·46094; R_C 32·53, R_D 32·72, R_F 33·22, $R_{G'}$ 33·61; $Mn_D^{20^\circ}$ 205·60. Densities determined: $d_{4^\circ}^{20^\circ}$ 1·1601, $d_{4^\circ}^{41\cdot2^\circ}$ 1·1353, $d_{4^\circ}^{64\cdot3^\circ}$ 1·1106, $d_{4^\circ}^{85\cdot6^\circ}$ 1·0850. Apparatus *A*.

15·1°	17·63	1·1657	38·48	303·6	61·3°	15·72	1·1141	32·80	305·2
26·9	17·25	1·1522	37·22	304·6	87·1	14·71	1·0832	29·84	306·8
41·7	16·56	1·1347	35·19	305·0				Mean	305·1

Dimethyl acetylenedicarboxylate, prepared by the acid, MeOH, C_6H_6, concentrated H_2SO_4 method, had b. p. 78·5°/4 mm., $d_{4^\circ}^{20^\circ}$ 1·1606, n_C 1·44380, n_D 1·44701, n_F 1·45498, $n_{G'}$ 1·46119; R_C 32·51, R_D 32·71, R_F 33·22, $R_{G'}$ 33·61; $Mn_D^{20^\circ}$ 205·63.

399. *Diethyl acetylenedicarboxylate.* B. p. 85·5°/2·5 mm.; *M* 170·16; n_C 1·43944, n_D 1·44245, n_F 1·44989, $n_{G'}$ 1·45573; R_C 41·96, R_D 42·22, R_F 42·83, $R_{G'}$ 43·31; $Mn_D^{20^\circ}$ 245·46. Densities determined: $d_{4^\circ}^{20^\circ}$ 1·0675, $d_{4^\circ}^{41\cdot4^\circ}$ 1·0459, $d_{4^\circ}^{60\cdot4^\circ}$ 1·0265, $d_{4^\circ}^{85\cdot9^\circ}$ 1·0009. Apparatus *D*.

14·3°	12·79	1·0732	33·90	382·6	61·5°	11·44	1·0254	28·97	385·0
21·7	12·62	1·0658	33·22	383·3	86·9	10·72	0·9999	26·47	386·0
41·9	11·98	1·0454	30·93	383·9				Mean	384·1

400. *Di-*n-*propyl acetylenedicarboxylate.* B. p. 116°/5 mm.; *M* 198·21; n_C 1·44329, n_D 1·44621, n_F 1·45344, $n_{G'}$ 1·45909; R_C 51·26, R_D 51·56, R_F 52·28, $R_{G'}$ 52·84; $Mn_D^{20^\circ}$ 286·65. Densities determined: $d_{4^\circ}^{20^\circ}$ 1·0256, $d_{4^\circ}^{40\cdot8^\circ}$ 1·0068, $d_{4^\circ}^{62\cdot1^\circ}$ 0·9875, $d_{4^\circ}^{85\cdot8^\circ}$ 0·9646. Apparatus *D*.

18·1°	12·78	1·0273	32·42	460·4	61·7°	11·56	0·9879	28·20	462·4
25·3	12·60	1·0208	31·76	461·0	87·4	10·84	0·9631	25·78	463·8
41·3	12·16	1·0063	29·94	460·8				Mean	461·6

401. *Diisopropyl acetylenedicarboxylate.* B. p. 96°/3 mm.; *M* 198·21; n_C 1·43621, n_D 1·43908, n_F 1·44623, $n_{G'}$ 1·45179; R_C 51·38, R_D 51·68, R_F 52·41, $R_{G'}$ 52·97; $Mn_D^{20^\circ}$ 285·24. Densities determined: $d_D^{20^\circ}$ 1·0090, $d_{4^\circ}^{42\cdot5^\circ}$ 0·9895, $d_{4^\circ}^{61\cdot5^\circ}$ 0·9725, $d_{4^\circ}^{86\cdot7^\circ}$ 0·9486. Apparatus *D*.

20·3°	12·26	1·0087	30·54	461·9	61·5°	11·18	0·9725	26·85	464·0
27·4	12·13	1·0015	30·00	463·2	87·5	10·39	0·9488	24·35	464·0
42·3	11·74	0·9897	28·72	463·6				Mean	463·3

402. *Di-*n-*butyl acetylenedicarboxylate.* B. p. 139°/5 mm.; *M* 226·28; n_C 1·44579, n_D 1·44861, n_F 1·45565, $n_{G'}$ 1·46106; R_C 60·36, R_D 60·69, R_F 61·52, $R_{G'}$ 62·15; $Mn_D^{20^\circ}$ 327·79. Densities determined: $d_{4^\circ}^{20^\circ}$ 0·9993, $d_{4^\circ}^{41\cdot4^\circ}$ 0·9820, $d_{4^\circ}^{62\cdot1^\circ}$ 0·9625, $d_{4^\circ}^{85\cdot7^\circ}$ 0·9431. Apparatus *D*.

16·0°	12·95	1·0027	32·07	537·0	61·4°	11·76	0·9639	27·99	540·0
30·3	12·58	0·9906	30·78	538·0	85·6	11·08	0·9432	25·81	540·7
41·0	12·31	0·9823	29·86	538·5				Mean	538·8

403. *Di*-n-*amyl acetylenedicarboxylate.* B. p. 143°/1·5 mm.; *M* 254·32; n_C 1·44858, n_D 1·45137, n_F 1·45826, $n_{G'}$ 1·46353; R_C 69·70, R_D 70·08, R_F 71·00, $R_{G'}$ 71·69; $Mn_D^{20°}$ 369·12. Densities determined: $d_{4°}^{20°}$ 0·9779, $d_{4°}^{40·8°}$ 0·9619, $d_{4°}^{62·5°}$ 0·9453, $d_{4°}^{85·7°}$ 0·9256. Apparatus *A*.

t.	*H.*	$d_{4°}^{t°}$.	γ.	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	γ.	*P.*
18·3°	17·16	0·9788	31·45	615·3	61·1°	15·79	0·9464	27·98	618·1
27·2	17·01	0·9723	30·97	617·1	86·1	14·92	0·9252	25·85	619·8
42·0	16·36	0·9610	29·44	616·4				Mean	617·7

404. *Diisoamyl acetylenedicarboxylate.* B. p. 133°/2·5 mm.; *M* 254·32; n_C 1·44842, n_D 1·45132, n_F 1·45825, $n_{G'}$ 1·46359; R_C 69·59, R_D 69·98, R_F 70·91, $R_{G'}$ 71·62; $Mn_D^{20°}$ 369·09. Densities determined: $d_{4°}^{20°}$ 0·9791, $d_{4°}^{41·4°}$ 0·9623, $d_{4°}^{61·6°}$ 0·9454, $d_{4°}^{86·5°}$ 0·9247. Apparatus *D*.

25·3°	12·57	0·9749	30·26	611·9	62·2°	11·61	0·9449	27·09	614·0
41·8	12·14	0·9620	28·84	612·6	86·4	10·98	0·9248	25·08	615·4
								Mean	613·5

405. *Ethyl phenylpropiolate.* B. p. 124°/6 mm.; n_C 1·54582, n_D 1·55231, n_F 1·56962, $n_{G'}$ 1·58458; R_C 52·20, R_D 52·71, R_F 54·07, $R_{G'}$ 55·24; $Mn_D^{20°}$ 270·40. Densities determined: $d_{4°}^{20°}$ 1·0563, $d_{4°}^{41·1°}$ 1·0381, $d_{4°}^{61·5°}$ 1·0209, $d_{4°}^{85·9°}$ 0·9999. Apparatus *A*.

14·2°	19·71	1·0613	39·17	410·6	40·9°	18·76	1·0383	36·47	412·3
21·1	19·38	1·0554	38·30	410·6	61·5	17·89	1·0209	34·20	412·6
21·7	19·32	1·0548	38·16	410·4	85·3	16·96	1·0004	31·77	413·4
								Mean	411·7

406. n-*Propyl phenylpropiolate.* B. p. 143°/7 mm.; *M* 188·22; n_C 1·53928, n_D 1·54464, n_F 1·56083, $n_{G'}$ 1·57480; R_C 56·99, R_D 57·45, R_F 58·86, $R_{G'}$ 60·07; $Mn_D^{20°}$ 290·72. Densities determined: $d_{4°}^{20°}$ 1·0352, $d_{4°}^{42·1°}$ 1·0168, $d_{4°}^{61·4°}$ 1·0003, $d_{4°}^{86·7°}$ 0·9793. Apparatus *A*.

13·9°	19·35	1·0403	37·69	448·3	41·8°	18·26	1·0171	34·78	450·0
18·6	19·18	1·0364	37·22	448·6	61·6	17·47	1·0003	32·72	450·0
28·5	18·86	1·0281	36·31	449·4	87·0	16·56	0·9791	30·36	451·2
								Mean	449·6

407. n-*Butyl phenylpropiolate.* B. p. 149°/5 mm.; *M* 202·24; n_C 1·53217, n_D 1·53802, n_F 1·55350, $n_{G'}$ 1·56676; R_C 61·41, R_D 61·97, R_F 63·45, $R_{G'}$ 64·70; $Mn_D^{20°}$ 311·05. Densities determined: $d_{4°}^{20°}$ 1·0208, $d_{4°}^{40·0°}$ 1·0056, $d_{4°}^{61·0°}$ 0·9892, $d_{4°}^{86·1°}$ 0·9684. Apparatus *A*.

19·3°	14·38	1·0213	36·27	485·7	41·9°	13·80	1·0041	34·22	487·1
22·0	14·32	1·0193	36·05	486·2	60·5	13·25	0·9896	32·38	487·5
27·2	14·18	1·0153	35·55	486·4	86·2	12·59	0·9683	30·11	489·2
								Mean	487·0

408. *Methyl cyanide.* B. p. 81°/757 mm.; *M* 41·05; n_C 1·34233, n_D 1·34408, n_F 1·34806, $n_{G'}$ 1·35087; R_C 11·04, R_D 11·09, R_F 11·21, $R_{G'}$ 11·29; $Mn_D^{20°}$ 55·18. Densities determined: $d_{4°}^{20°}$ 0·7843, $d_{4°}^{40·4°}$ 0·7639, $d_{4°}^{60·4°}$ 0·7429. Apparatus *A*.

19·1°	20·03	0·7852	29·45	121·8	40·6°	18·66	0·7637	26·68	122·2
26·7	19·50	0·7776	28·40	121·9	60·4	17·40	0·7429	24·20	122·7
								Mean	122·1

[Merckx, Verhulst, and Bruylants (*Bull Soc. chim. Belg.*, 1933, **42**, 777) found $d_{4°}^{20°}$ 0·7820, $n_D^{20°}$ 1·34381 when extrapolated from data at 15° and 30°.]

409. *Ethyl cyanide.* B. p. 97°/758 mm.; *M* 55·08; n_C 1·36398, n_D 1·36578, n_F 1·37016, $n_{G'}$ 1·37327; R_C 15·68, R_D 15·75, R_F 15·92, $R_{G'}$ 16·04; $Mn_D^{20°}$ 75·23. Densities determined: $d_{4°}^{20°}$ 0·7828, $d_{4°}^{41·4°}$ 0·7618, $d_{4°}^{61·9°}$ 0·7418. Apparatus *D*.

19·9°	14·08	0·7829	27·22	160·7	41·3°	13·24	0·7619	24·91	161·6
28·3	13·85	0·7745	26·49	161·3	60·7	12·31	0·7430	22·59	161·7
								Mean	161·4

[Bruylants *et al.* found $d_{4°}^{20°}$ 0·7817, $n_D^{20°}$ 1·36585].

410. n-*Propyl cyanide.* B. p. 118°/757 mm.; *M* 69·11; n_C 1·38232, n_D 1·38423, n_F 1·38885, $n_{G'}$ 1·39221; R_C 20·35, R_D 20·43, R_F 20·65, $R_{G'}$ 20·81; $Mn_D^{20°}$ 95·66. Densities determined: $d_{4°}^{20°}$ 0·7913, $d_{4°}^{40·8°}$ 0·7742, $d_{4°}^{60·6°}$ 0·7559, $d_{4°}^{85·3°}$ 0·7328. Apparatus *D*.

20·1°	14·03	0·7912	27·41	199·9	60·1°	12·39	0·7563	23·14	200·4
28·4	13·75	0·7841	26·62	200·2	85·7	11·44	0·7325	20·69	201·5
41·0	13·23	0·7740	25·29	200·2				Mean	200·4

[Bruylants *et al.* found $d_{4°}^{20°}$ 0·7909, $n_D^{20°}$ 1·38385.]

411. n-*Butyl cyanide.* B. p. 141°/764 mm.; *M* 83·13; n_C 1·39492, n_D 1·39690, n_F 1·40168, $n_{G'}$ 1·40505; R_C 24·93, R_D 25·04, R_F 25·31, $R_{G'}$ 25·50; $Mn_D^{20°}$ 116·12. Densities determined: $d_{4°}^{20°}$ 0·7992, $d_{4°}^{41·0°}$ 0·7834, $d_{4°}^{60·3°}$ 0·7667, $d_{4°}^{80·6°}$ 0·7437. Apparatus *D*.

t.	*H.*	$d_{4}^{t°}$.	γ.	*P.*	*t.*	*H.*	$d_{4}^{t°}$.	γ.	*P.*
20·0°	13·90	0·7992	27·43	238·1	61·6°	12·42	0·7657	23·49	239·0
24·6	13·79	0·7955	27·09	238·4	86·5	11·56	0·7438	21·23	239·9
40·6	13·07	0·7837	25·30	237·9				Mean	238·7

[Bruylants *et al.* found $d_{4}^{20°}$ 0·7992, $n_{D}^{20°}$ 1·39711.]

412. n-*Amyl cyanide.* B. p. 162°/777 mm.; *M* 97·16; n_{C} 1·40481, n_{D} 1·40687, n_{F} 1·41183, $n_{G'}$ 1·41543; R_{C} 29·58, R_{D} 29·72, R_{F} 30·03, $R_{G'}$ 30·26; $Mn_{D}^{20°}$ 136·69. Densities determined: $d_{4}^{20°}$ 0·8047, $d_{4}^{40·7°}$ 0·7901, $d_{4}^{61·7°}$ 0·7733, $d_{4}^{86·2°}$ 0·7526. Apparatus *A*.

23·2°	18·32	0·8023	27·52	277·4	61·2°	16·62	0·7737	24·08	278·2
28·4	18·14	0·7984	27·12	277·6	86·8	15·47	0·7521	21·79	279·1
41·0	17·50	0·7898	25·88	277·5				Mean	278·0

[Bruylants *et al.* found $d_{4}^{20°}$ 0·8053, $n_{D}^{20°}$ 1·40694.]

413. iso*Amyl cyanide.* B. p. 153·5°/756 mm.; *M* 97·16; n_{C} 1·40391, n_{D} 1·40592, n_{F} 1·41092, $n_{G'}$ 1·41462; R_{C} 29·59, R_{D} 29·72, R_{F} 30·04, $R_{G'}$ 30·28; $Mn_{D}^{20°}$ 136·60. Densities determined: $d_{4}^{20°}$ 0·8030, $d_{4}^{41·6°}$ 0·7869, $d_{4}^{61·3°}$ 0·7707, $d_{4}^{86·8°}$ 0·7495. Apparatus *A*.

20·5°	17·89	0·8026	26·89	275·7	61·0	16·04	0·7703	23·15	276·5
27·1	17·83	0·7975	26·63	276·8	87·0	14·96	0·7493	20·99	277·5
41·6	17·00	0·7869	25·05	276·2				Mean	276·5

414. n-*Hexyl cyanide.* B. p. 182—182·5°/757 mm.; *M* 111·18; n_{C} 1·41200, n_{D} 1·41406, n_{F} 1·41914, $n_{G'}$ 1·42285; R_{C} 34·15, R_{D} 34·31, R_{F} 34·67, $R_{G'}$ 34·95; $Mn_{D}^{20°}$ 157·22. Densities determined: $d_{4}^{20°}$ 0·8100, $d_{4}^{40·8°}$ 0·7945, $d_{4}^{60·9°}$ 0·7796, $d_{4}^{85·0°}$ 0·7597. Apparatus *A*.

21·3°	18·10	0·8089	27·42	314·5	62·5°	16·34	0·7777	23·80	315·7
41·8	17·16	0·7934	25·49	314·9	85·0	15·46	0·7597	21·99	316·9
								Mean	315·3

The surface-tension measurements were somewhat erratic and not always accurately reproducible; some selected results are given above. The results cannot be regarded as more than approximate, consequently the parachor values are untrustworthy.

[Bruylants *et al.* found $d_{4}^{20°}$ 0·8096, $n_{D}^{20°}$ 1·41419.]

415. *Allyl cyanide.* B. p. 118·5°/753 mm.; *M* 67·09; n_{C} 1·40342, n_{D} 1·40593, n_{F} 1·41214, $n_{G'}$ 1·41678; R_{C} 19·56, R_{D} 19·67, R_{F} 19·93, $R_{G'}$ 20·13; $Mn_{D}^{20°}$ 94·32. Densities determined: $d_{4}^{20°}$ 0·8377, $d_{4}^{41·6°}$ 0·8163, $d_{4}^{60·6°}$ 0·7988, $d_{4}^{85·9°}$ 0·7739. Apparatus *D*.

13·4°	14·37	0·8441	29·96	186·0	42·0°	13·28	0·8159	26·76	187·0
17·1	14·25	0·8406	29·58	186·1	62·1	12·51	0·7973	24·63	187·5
21·2	14·10	0·8365	29·13	186·3	87·5	11·51	0·7723	21·95	188·0
								Mean	187·8

416. *Trimethylene dicyanide.* B. p. 140°/8 mm.; *M* 94·12; n_{C} 1·42728, n_{D} 1·42947, n_{F} 1·43492, $n_{G'}$ 1·43880; R_{C} 24·48, R_{D} 24·59, R_{F} 24·80, $R_{G'}$ 25·05; $Mn_{D}^{20°}$ 134·55. Densities determined: $d_{4}^{20°}$ 0·9879, $d_{4}^{41·1°}$ 0·9721, $d_{4}^{61·2°}$ 0·9575, $d_{4}^{85·0°}$ 0·9398. Apparatus *D*.

16·0°	19·66	0·9909	48·11	250·2	60·6°	18·33	0·9579	43·36	252·1
41·0	19·04	0·9720	45·70	251·8	86·1	17·52	0·9390	40·62	253·1
								Mean	251·8

The surface-tension measurements presented some difficulty, possibly because the liquid did not wet the glass too well. The results for γ and hence for *P* must be regarded as approximate only; it is hoped to repeat the measurements by the maximum bubble-pressure method.

417. *Phenyl cyanide.* B. p. 189°/758 mm.; *M* 103·12; n_{C} 1·52283, n_{D} 1·52823, n_{F} 1·54208, $n_{G'}$ 1·55346; R_{C} 31·31, R_{D} 31·58, R_{F} 32·27, $R_{G'}$ 32·83; $Mn_{D}^{20°}$ 157·59. Densities determined: $d_{4}^{20°}$ 1·0058, $d_{4}^{40·3°}$ 0·9885, $d_{4}^{60·5°}$ 0·9713, $d_{4}^{86·6°}$ 0·9486. Apparatus *A*.

19·3°	20·97	1·0064	39·52	256·9	61·2°	19·03	0·9707	34·59	257·6
27·0	20·53	0·9998	38·43	256·8	87·0	17·80	0·9483	31·61	257·8
40·9	20·01	0·9880	37·02	257·4				Mean	257·3

418. *Benzyl cyanide.* B. p. 108·5°/15 mm.; *M* 117·15; n_{C} 1·51830, n_{D} 1·52271, n_{F} 1·53161, $n_{G'}$ 1·54260; R_{C} 34·97, R_{D} 35·22, R_{F} 35·72, $R_{G'}$ 36·34; $Mn_{D}^{20°}$ 178·38. Densities determined: $d_{4}^{20°}$ 1·0155, $d_{4}^{40·5°}$ 1·0013, $d_{4}^{60·1°}$ 0·9860, $d_{4}^{86·6°}$ 0·9659. Apparatus *D*.

19·5°	16·80	1·0159	42·15	293·8	60·3°	15·48	0·9861	37·71	294·3
27·3	16·60	1·0102	41·42	294·1	86·3	14·47	0·9657	34·51	294·0
40·5	16·19	1·0013	40·04	294·3				Mean	294·1

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135. *Synthesis of Some Derivatives of* 3 : 4-*Diphenyl*-n-*hexane.*

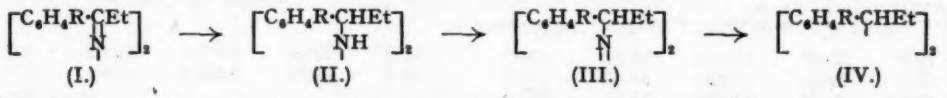
By Gábor Fodor and János Wein.

The two isomeric *pp'*-diamino-3 : 4-diphenyl-*n*-hexanes (IV; R = NH_2) were synthesised from p-*amino*- (I; R = NH_2) and p-*acetamido-propiophenoneazine* (I; R = NHAc) respectively by a route, (I) → (II) → (III) → (IV), employed first for the synthesis of hexœstrol (IV; R = OH) *via* its dimethyl ether by Földi and Fodor (*Ber.*, 1941, **74**, 589; cf. French Pat. 872,504; Hung. Priority 3 Jan., 1939; cf. Gilman, "Organic Chemistry", 1945, II, p. 1485, and Bretschneider *et al.*, *Ber.*, 1941, **74**, 571). The steric configuration of these diamines was established by their conversion into *meso*- and *iso*-hexœstrol respectively (IV; R = OH). The *pp'*-diamino-3 : 4-diphenyl-*n*-hexanes and hexœstrol had been prepared in a similar way by Baker (*J. Amer. Chem. Soc.*, 1943, **65**, 1572) from *p*-propionamidopropiophenone azine, but no record of this paper had been available in Hungary. A new preparation of the two isomeric 3 : 4-diphenyl-*n*-hexanes (IV; R = H) by the azine route is also described. The crystalline isomer was converted *via* the pp'-*dinitro*- (IV; R = NO_2) and the pp'-*dibromo*-derivative (IV; R = Br) into the *meso-pp'*-diaminodiphenyl-*n*-hexane; the liquid 3 : 4-diphenyl-*n*-hexane yields by an analogous treatment the racemic diamine (IV; R = NH_2). The meso-NN'-*dicarbethoxy*-derivative (IV, R = NH·CO_2Et) was also prepared.

In continuation of the work on 3 : 4-diphenyl-*n*-hexanes (Földi and Fodor, *loc. cit.*), we set out to synthesise some amino-analogues of synthetic sex hormones, especially as Lettré (*Z. physiol. Chem.*, 1943, **276**, 206) had found an amino-derivative of a natural hormone (equilin) to possess a high antimitotic activity. At first, *pp'*-diamino-3 : 4-diphenyl-*n*-hexane, an amino-analogue of hexœstrol, was prepared. This compound had been mentioned by Carlisle and Crowfoot (*J.*, 1941, 6; *Chem. Zentr.*, 1941, II, 1499), and Baker (*loc. cit.*) had recorded the preparation of these diamines by the ketazine route from *p*-propionamidopropiophenone, but we now record our results briefly, especially the preparation of new compounds, as our yields are better than Baker's (*loc. cit.*).

p-Acetamidopropiophenone azine (I; R = NH·Ac; for ketone, see Kunckell, *Ber.*, 1900, **33**, 2643) was converted *via* (II) into (III), an arylaliphatic azo-compound of relatively great stability (cf. ω-azotoluene, Thiele, *Annalen*, 1910, **376**, 265; Földi and Fodor, *loc. cit.*); at 240° it decomposed with evolution of nitrogen, yielding a mixture of the two stereoisomeric *pp'*-diacetamido-3 : 4-diphenyl-*n*-hexanes, separated by crystallisation. The sparingly soluble, higher-melting isomer was deacetylated by means of alcoholic potassium hydroxide, and the more soluble, lower-melting form by 3N-hydrochloric acid, to the corresponding diamines (IV; R = NH_2), m. p. 136—137° and 80° (uncorr.) respectively; Carlisle and Crowfoot (*loc. cit.*) record m. p. 140° for the *meso*-compound, but 98° for the racemate; Baker (*loc. cit.*) reported lower m. p.s, 132—134° and 63—65°, probably owing to incomplete separation of the two stereoisomers. We are unable to account for this discrepancy in the m. p. of the racemate as the method of the preparation of Carlisle and Crowfoot's compound, m. p. 98°, is unknown to us.

The steric configuration of the diamines is elucidated by the fact that the higher-melting isomer was converted by the diazo-method (cf. Baker, *loc. cit.*) into *meso*hexœstrol (Wessely and Welleba, *Ber.*, 1941, **74**, 777; cf. Carlisle and Crowfoot, *loc. cit.*); it is consequently *meso-pp'*-diamino-3 : 4-diphenyl-*n*-hexane; the lower-melting isomer similarly afforded the racemic *iso*hexœstrol (resolution by Wessely and Welleba, *loc. cit.*), and is therefore the racemic compound.



By the same azine method, 4-aminopropiophenone (Kunckell, *loc. cit.*) was converted into the same *meso*-diamine, without isolation of any intermediates except the ketazine.

Finally, the steroisomeric 3 : 4-diphenyl-*n*-hexanes (IV; R = H), prepared from 1-bromopropylbenzene with ethylmagnesium bromide (Späth, *Monatsh.*, 1913, **34**, 2010) or with sodium (Lepin and Reich, *J. Russ. Phys. Chem. Soc.*, 1915, **47**, 154, 158), or from benzaldazine with ethylmagnesium bromide (Busch and Fleischmann, *Ber.*, 1910, **43**, 748), was prepared by the azine method from propiophenone azine (I; R = H) *via* 1 : 1-*diphenylazopropane* (III; R = H). Nitration of the "solid" 3 : 4-diphenyl-*n*-hexane led *via pp'*-dinitro-3 : 4-diphenyl-*n*-hexane (IV; R = NO_2) to the *meso*-diamine (IV; R = NH_2). The "liquid" 3 : 4-diphenylhexane similarly gave the racemic diamine (IV; R = NH_2). The "solid form" of diphenylhexane proved to be the *meso*-, and the "liquid form" the racemic compound (cf. Carlisle and Crowfoot, *loc. cit.*).

Another preparation of the *meso*-diamine was effected by bromination of the *meso*-compound (IV; R = H) to (IV; R = Br) (see Barber and Slack, *J.*, **1944**, 613), followed by treatment with aqueous ammonia under pressure at 200°.

meso-pp'-Diamino-3 : 4-diphenyl-*n*-hexane was assayed by Dr. L. Rigó by the Allen–Doisy test, and the results will be published elsewhere. However, Dodds *et al.* (*Proc. Roy. Soc.*, **1944**, *B*, **132**, 83) show that this compound has a low œstrogenic activity (100 rat units per g.).

pp'-Diamino-3 : 4-diphenylhex-3-ene, an amino-analogue of stilbœstrol, has also a low œstrogenic activity (Vargha and Kovács, *Ber.*, **1942**, **75**, 794). The hexane analogue will be examined by different tests for antimitotic and anticarcinogenic activity.

The NN'-*dicarbethoxy*-derivative (IV; R = NH·CO_2Et) was also prepared in view of the influence of some amino-*s*-diarylethylenes, -arylurethanes, and other aromatic amines upon experimental animal tumours (*Ann. Rep. British Empire Cancer Campaign*, **1946**, **25**; cf. Boyland, *Biochem. J.*, **1946**, **40**, 55).

Experimental.

(All m. p.s are uncorrected.)

p-*Acetamidopropiophenone Azine* (I; R = NHAc).—*p*-Acetamidopropiophenone (90·5 g.) was dissolved in hot alcohol (300 c.c.), and hydrazine hydrate (25 c.c.) and glacial acetic acid (20 c.c.) added. The mixture was refluxed for 15 mins. on a steam-bath, and the *azine* crystallised. After cooling, filtration, and washing with alcohol, it had m. p. 268—270° (84 g.; 93%). The product is pure, but may be recrystallized from nitrobenzene (Found : C, 69·65; H, 6·98. $C_{22}H_{26}O_2N_4$ requires C, 69·8; H, 6·9%).

p-*Aminopropiophenone Azine* (I; R = NH_2).—The ketone (5 g.) was dissolved in hot methanol (25 c.c.), and hydrazine hydrate (1 c.c.) and glacial acetic acid (1·5 c.c.) added; the mixture was boiled for 30 mins. on the steam-bath, then diluted with water (25 c.c.) and cooled. The *ketazine* (4·6 g.) separated as golden-yellow crystals, m. p. 140—141° (Found : C, 73·8, 73·8; H, 7·3, 7·8. $C_{18}H_{22}N_4$ requires C, 73·9; H, 7·5%).

pp'-*Diacetamido*-s-*bis*-(1-*phenylpropyl*)*hydrazine* (II; R = NHAc).—A suspension of the foregoing ketazine (38 g.) in ethanol (1400 c.c.) was stirred in the presence of palladium–charcoal catalyst (4 g., containing 20% $PdCl_2$, and saturated previously with hydrogen) in a three-necked flask connected with a source of hydrogen under atmospheric pressure, at 60°. After 6 hrs., 5400 c.c. of hydrogen had been absorbed (theor., 4400 c.c.), and a colourless solution obtained; the catalyst was filtered off, and a portion of the filtrate evaporated to dryness in a vacuum (with a stream of hydrogen passing through a capillary); white crystals (2 g.) resulted, m. p. 178—185°, and could be recrystallised from methanol–water (1 l.) in an atmosphere of hydrogen as it is very sensitive to oxygen. The greater part of the solution was transformed into the corresponding azo-compound (below).

s-*Di*-1 : 1'-(p-*acetamidophenyl*)*azopropane* (III; R = NHAc).—(*a*) Anhydrous potassium acetate (20 g.) was added to a solution of the foregoing hydrazo-compound (35 g.) in alcohol (1500 c.c.) cooled to 5°, and iodine (22 g.) added slowly. The iodine was decolorised and a crystalline solid separated; this was filtered off (23 g.), and the mother-liquor poured into water, affording a second crop (7 g.), and the filtrate, when evaporated until alcohol-free, gave a further 4 g. of the *azo*-compound. After recrystallisation from *n*-butanol, colourless crystals resulted which underwent partial decomposition at 200—260° (Found : C, 70·0; H, 7·3. $C_{22}H_{28}O_2N_4$ requires C, 69·4; H, 7·4%).

(*b*) The hydrazo-compound (23·4 g.) in alcohol (1500 c.c.) was mechanically stirred in an atmosphere of oxygen in the presence of 2N-sodium hydroxide (1·7 c.c.) and 10% copper sulphate solution (1·7 c.c.); 970 c.c. of oxygen were absorbed (theor., 990 c.c.); the azo-compound crystallised, and was filtered off and dried (10 g.), m. p. 200—300° (evolution of nitrogen). The mother-liquor on evaporation afforded a further 13 g. of the same compound.

pp'-*Diacetamido*-3 : 4-*diphenyl*-n-*hexane* (IV; R = NHAc).—The foregoing azo-compound (5·5 g.), suspended in diphenyl ether (5·5 c.c.), was heated in an air-bath to 240°; between 200° and 240° nitrogen was evolved (300 c.c., theor., 320 c.c.). After cooling, the mixture was treated with cold methanol (10 c.c.), filtered, washed with methanol (10 c.c.), and dried; white crystals (2·0 g.) of meso-pp'-*diacetamido*-3 : 4-*diphenyl*-n-*hexane* were obtained. After recrystallisation from ethyl acetoacetate or nitrobenzene, they had m. p. 318—321° (Found : C, 75·1; H, 8·4; N, 7·95. $C_{22}H_{28}O_2N_2$ requires C, 75·0; H, 8·0; N, 8·0%).

The methanolic mother-liquor was evaporated in a vacuum to dryness; the partly crystalline residue was dissolved in ether (10 c.c.) and cooled, and the resulting crystals were filtered off, washed with ether (20 c.c.) and dried (2·2 g.). After recrystallisation from alcohol–water, the racemic diacetamido-compound, had m. p. 190° (Found : C, 75·0; H, 8·0%).

pp'-*Diamino*-3 : 4-*diphenyl*-n-*hexane* (IV; R = NH_2).—(a) *From the corresponding acetamido-compound.* The acetamido-compound (2·5 g.; m. p. 320°) was boiled with alcohol (72·5 c.c.) and potassium hydroxide (14·5 g.) in a water-bath for 6 hrs., evaporated in a vacuum to dryness, and water (25 c.c.) added to the crystalline residue; the crystals (1·9 g.) were filtered off, and recrystallised from diluted alcohol (50%), or benzene–light petroleum (1 : 1); colourless prisms, m. p. 136—137°, of the *meso*-form were obtained.

Hydrochloride. The base (0·27 g.) was dissolved in 0·1N-hydrochloric acid (20 c.c.), and the solution cooled with ice and saturated with hydrogen chloride. The *dihydrochloride* (0·30 g.) crystallised in glistening needles, m. p. 338° (Found : C, 63·5; H, 7·9. $C_{18}H_{24}N_2,2HCl$ requires C, 63·3; H, 7·7%).

The racemic diamino-compound (0·7 g.) was obtained by heating the diacetamido-diphenylhexane (m. p. 190°) (1 g.) for 4 hrs. with 3N-hydrochloric acid (40 c.c.) and neutralising with ammonia; needles (from aqueous methanol), m. p. 80° (Found : C, 80·6; H, 9·0. Calc. for $C_{18}H_{24}N_2$: C, 80·5; H, 9·0%).

(b) *From* p-*aminopropiophenone azine* (I; R = NH_2). The solution of the amino-ketazine (5·98 g.)

in methanol (110 c.c.) and palladium–charcoal catalyst (0·5 g.) were shaken with hydrogen at room temperature and pressure. After 10 hrs. 870 c.c. of hydrogen had been absorbed (theor., 870 c.c.) and a colourless solution resulted. Anhydrous potassium acetate (4 g.) was added, the mixture cooled to 0°, and iodine (5 g.) added in small portions; the solution was diluted with water (300 c.c.), neutralised with potassium carbonate, and extracted with ether. The residue left on evaporation of the ether, a pale yellow oil, was heated in high vacuum in an oil-bath to 170°, nitrogen being evolved. The product yielded after recrystallisation from alcohol a small quantity of the *meso*-diamino-compound, m. p. 136—137° alone and mixed with the specimen obtained as in (a).

(c) *From* pp′-*dinitro*-3 : 4-*diphenyl*-n-*hexane* (IV; R = NO_2). (1) The dinitro-compound (2 g.; m. p. 170°) in alcohol (145 c.c.) was added to a suspension of palladium–charcoal catalyst (1 g.) in alcohol (20 c.c.), saturated previously with hydrogen, and shaken at room temperature and pressure. After 7 hrs., 830 c.c. of hydrogen had been absorbed (theor., 820 c.c.), and 4N-hydrogen chloride in anhydrous alcohol (6 c.c.) was then added, and the solution evaporated to dryness. The crystalline hydrochloride was recrystallised from alcohol and yielded 1·03 g. of pure hydrochloride, m. p. 332° alone and mixed with a specimen obtained as in (a). The mother-liquor yielded, after evaporation, recrystallisation, and neutralisation, a further 0·47 g. of the *meso*-diamino-compound, m. p. and mixed 136—137°.

(2) The vacuum-distilled dinitro-compound (4 g.) from liquid 3 : 4-diphenyl-*n*-hexane was dissolved in alcohol (100 c.c.) and hydrogenated catalytically as above. The resulting hydrochloride crystallised with difficulty; it was basified, the amino-compound extracted with ethyl acetate, the solvent evaporated, and the residual oil acetylated with acetic anhydride (10 c.c.) by heating on a water-bath; after evaporation, the acetyl compound was crystallised from aqueous acetic acid (1 : 1). Crystals of racemic *pp′*-diacetamido-3 : 4-diphenyl-*n*-hexane were isolated, m. p. 190—191° alone and mixed with an authentic specimen.

(d) *From* pp′-*dibromo*-3 : 4-*diphenyl*-n-*hexane*. The dibromo-compound, m. p. 168° (400 mg.), cuprous iodide (40 mg.), and concentrated aqueous ammonia (12 c.c.) were heated in a sealed tube to 205°. After 10 hrs. the tube was opened, the crystals (295 mg.) filtered off, treated with 0·1N-hydrochloric acid (20 c.c.), filtered from unchanged bromo-compound (175 mg.), then neutralised with concentrated ammonia. The *meso*-diamino-compound (100 mg.) was obtained, m. p. and mixed m. p. with the compound prepared as in (a) 136—137°.

1 : 1′-*Diphenylazopropane* (III; R = H).—Propiophenone azine (17 g.) was suspended in alcohol, added to a palladium–charcoal catalyst (1 g.) saturated with hydrogen, and shaken with hydrogen at 60° under atmospheric pressure. After 6 hrs. the theoretical quantity of hydrogen had been absorbed. The colourless solution of the hydrazo-compound was treated in the usual manner with iodine, and poured into water; a colourless oil and white crystals separated. The latter had m. p. 55° after recrystallisation from light petroleum (Found: C, 81·0; H, 8·3; N, 10·6. $C_{18}H_{22}N_2$ requires C, 81·2; H, 8·2; N, 10·5%), and both these and the liquid, on thermal decomposition, afforded a mixture of the two isomeric 3 : 4-diphenyl-*n*-hexanes, as follows.

3 : 4-*Diphenyl*-n-*hexane* (IV; R = H).—The reaction mixture obtained in the preceding experiment (16 g.) was heated to 170°; the theoretical volume (1200 c.c.) of nitrogen was evolved, and the residue was distilled in vacuum. 5 G. of lower-boiling by-product were followed by 7·5 g. of the isomers (IV; R = H), which were separated in the usual manner; the solid, *meso*-form, recrystallised from alcohol, had m. p. 92° (cf. Kohler, *Amer. Chem. J.*, 1906, **35**, 395). The liquid form was distilled; b. p. 298° (cf. Lepin and Reich, *loc. cit.*).

pp′-*Dinitro*-3 : 4-*diphenyl*-n-*hexane* (IV; R = NO_2).—(1) meso-*Form*.—The *meso*-diphenylhexane (5 g.) was added in small portions to concentrated ice-cold nitric acid (50 c.c.). The brown solution was kept for 5 mins. at 0°, then poured into ice-water (400 g.); pale yellow crystals separated. Recrystallised twice from glacial acetic acid, the pure *dinitro*-derivative (2·79 g.) was obtained, m. p. 170° (Found: C, 65·6; H, 6·3. $C_{18}H_{20}O_4N_2$ requires C, 65·8; H, 6·15%). From the mother-liquor of the recrystallisation a *trinitro*-derivative (probably the 2 : 2′ : 4-trinitro-compound) (2·18 g.) was isolated, m. p. 126—127° (Found: C, 57·7; H, 5·4. $C_{18}H_{19}O_6N_3$ requires C, 57·9; H, 5·1%).

Nitration of *meso*-3 : 4-diphenyl-*n*-hexane in concentrated sulphuric acid yielded another *trinitro*-derivative (probably 2 : 4 : 4′-trinitro-); pale yellow plates from glacial acetic acid, m. p. 217—218° (Found: N, 11·3. $C_{18}H_{19}O_6N_3$ requires N, 11·3%).

(2) *Racemic form*. Liquid 3 : 4-diphenyl-*n*-hexane (5 g.) was added as above to concentrated nitric acid (40 c.c.) with cooling; the brown solution was kept for 5 mins. at 0°, and then poured into water. The resulting oil was extracted with chloroform, washed with sodium hydrogen carbonate solution until neutral, dried, and distilled at 250° (air-bath temp.)/8—10 mm. The resulting yellow oil was reduced to the amino-compound as described above.

meso-pp′-*Dibromo*-3 : 4-*diphenyl*-n-*hexane* (IV; R = Br).—*meso*-3 : 4-Diphenyl-*n*-hexane (230 mg.) was fused, and bromine (0·12 c.c.) added dropwise with stirring. Hydrogen bromide was evolved, and the resulting red-brown mixture (380 mg.) was recrystallised from alcohol (15 c.c.), forming glistening, colourless needles (160 mg.), m. p. 163°. Recrystallisation from alcohol (15 c.c.) gave 100 mg., m. p. 168°. Barber and Slack (*loc. cit.*) recorded m. p. 170—172° (Found: C, 55·2; H, 5·0. Calc. for $C_{18}H_{20}Br_2$: C, 54·6; H, 5·1%).

Hexœstrol (meso-pp′-*Dihydroxy*-3 : 4-*diphenyl*-n-*hexane*) (IV; R = OH).—The *meso*-diamino-compound (2·1 g.) was dissolved in a solution of sulphuric acid (11·8 g.) in water (850 c.c.), and on cooling, the sulphate crystallised in micro-crystals. The suspension was cooled to 0° and 2% aqueous sodium nitrite (60·7 c.c.) was added dropwise (30 mins.) with stirring. Diazotisation was complete in 1 hr., and the solution was then rapidly heated to boiling; nitrogen was evolved at 85°, and a crystalline solid separated. This was crude hexœstrol (2 g., dry), m. p. 182—183°. After recrystallisation from benzene, it had m. p. 186° (Found: C, 80·1; H, 8·05. Calc. for $C_{18}H_{22}O_2$: C, 80·0; H, 8·2%).

iso*Hexœstrol* (*Racemic* pp′-*Dihydroxy*-3 : 4-*diphenyl*-n-*hexane*) (IV; R = OH).—The racemic diamino-compound (0·1 g.) was dissolved in 5% sulphuric acid (10 c.c.), 2% sodium nitrite solution (2·6 c.c.) added dropwise with cooling to + 2°, and the mixture kept for 1 hr. at this temperature. Then sulphuric acid (1 g.) and a trace of sodium sulphite were added, followed by rapid heating to boiling. The phenolic

product separated as a brown solid. After distillation at 150—170°/0·02 mm., it melted at 125—126° alone and on admixture with an authentic specimen.

meso-pp'-*Biscarbethoxyamino*-3 : 4-*diphenyl*-n-*hexane* (IV; R = NH·CO_2Et).—The *meso*-diamino-compound (268 mg.) and ethyl chloroformate (2 g.) were heated on a water-bath, the unchanged ester evaporated, and the residue treated with water and filtered off. The crystalline product (348 mg.) had m. p. 198—200°, increased by recrystallisation from ethanol to 200°; it was soluble in hot alcohol, insoluble in water (Found : C, 69·9; H, 7·7. $C_{34}H_{32}O_4N_2$ requires C, 69·9; H, 7·8%).

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136. *Preparation of Unsymmetrical Carbocyanines.*

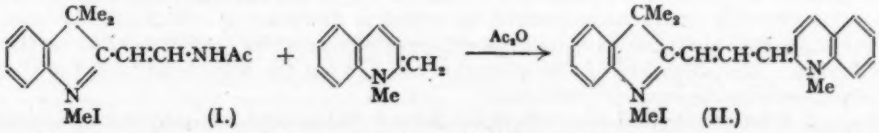
By J. D. KENDALL and J. R. MAJER.

The quaternary alkyl *p*-toluenesulphonates of a number of heterocyclic bases containing reactive methyl or methylene groups have been condensed with esters of trithio-orthoformic acid in acid anhydride solution to give compounds which contain the group >C : CH·SR (R = alkyl or aralkyl). These compounds react in the presence of bases, with compounds containing a reactive methyl or methylene group to yield cyanine dyes.

THE first unsymmetrical carbocyanines were prepared by the action of an alkali and an oxidising agent on quaternary salts of 2 : 4-dimethylquinoline or its substitution products (D.R.-P. 155,541). The blue dyes were called " dicyanines ", and their preparation was investigated by later workers (Wise and Adams, *Amer. J. Eng. Chem.*, 1918, **10**, 801; Mikesko, Haller, and Adams, *J. Amer. Chem. Soc.*, 1920, **42**, 2392; O. Fischer, *J. pr. Chem.*, 1918, **98**, 209), but it was not until 1924 that Mills and Odams showed that dicyanines were derivatives of 2 : 4'-carbocyanine (*J.*, 1924, 1916). Mills and Odams prepared the parent 1 : 1'-diethyl-2 : 4'-carbocyanine iodide by treating a mixture of lepidine and quinaldine ethonitrates with di-*o*-formylmethylamino-diphenyl disulphide and pyridine and separating the dicyanine from its congeners.

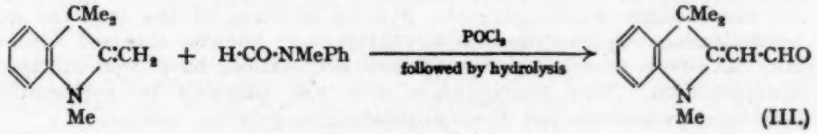
These methods were applicable only to quinoline derivatives, and the central methine group was believed to be provided by the breakdown of one of the quaternary salts. Later methods were directed to the condensation of derivatives of formic acid with two different quaternary salts in a step-wise fashion, the formic acid derivative providing a central methine group for the unsymmetrical carbocyanine dye.

The first of these methods (Soc. Chem. Ind. Basle, B.P. 334,706, 1928) suggested the use of formiminoethyl ether hydrochloride. This was condensed with Fischer's base in acetic acid–acetic anhydride followed by treatment with aqueous potassium iodide. The resulting intermediate 1 : 3 : 3-trimethyl-2-2'-acetamidovinylindolenine iodide (I) was boiled with *N*-methyl-2-methylene-2 : 3-dihydroquinoline in acetic anhydride to yield the unsymmetrical carbocyanine (II). Similar intermediates were prepared later from formamide or thioformamide (Knott, Kodak, B.P. 577,549).



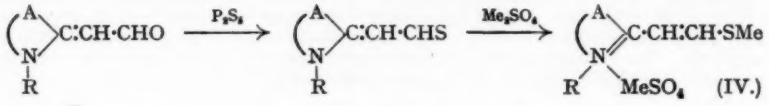
Piggott and Rodd found that related intermediates of this type and carbocyanine dyes could be prepared by the use of diaryl formamidines (I.C.I., B.P.P. 344,409; 354,898); the intermediates, which contained 2-arylamino- or -acetarylamido-vinyl groups, also reacted with indoles and formed dyes with pyrazolones (B.P.P. 353,863, 366,904). Knott found that this type of intermediate could also be prepared from *iso*formanilide (*J.*, 1946, 120).

Other formic acid derivatives, *e.g.*, *N*-methylformanilide were found to yield reactive intermediates by first reacting in phosphorus oxychloride solution with α-methyleneindoline bases of the type of Fischer's base and subsequent alkaline hydrolysis (I.G., B.P. 438,278). By this method heterocyclic aldehydes were formed, *e.g.*, 1 : 3 : 3-trimethyl-2-formylmethyleneindole (III).



These aldehydes likewise yielded carbocyanines on condensation with methylene bases in phosphorus oxychloride solution (I.G., B.P. 438,603) or with quaternary salts in pyridine solution (I.G., B.P. 442,160).

Corresponding ω-aldehydes containing the thiazole ring were prepared later by Kodak (B.P. 466,245) and used in the synthesis of unsymmetrical carbocyanines (B.P. 466,246) and merocyanines (B.P. 466,244). Other workers attempted to increase the reactivity of the aldehydes by converting them into their semicarbazones and thiosemicarbazones (I.G., B.P. 510,242), and into methylthio-compounds (IV) by heating them with phosphorus pentasulphide to give thioaldehydes which were then converted into quaternary salts with methyl sulphate (Kumetat and Riester, U.S.P. 2,349,179). Like the corresponding compounds with α-thioether groupings (Kendall, B.P. 424,559) these intermediates, which contained the vinylogous 2-methylthiovinyl groupings, were very reactive and of great value in the preparation of the unsymmetrical carbocyanines (V) (Kumetat and Riester, U.S.P. 2,354,524). Their method of preparation *via* the aldehydes, however, was not simple and the yields were poor.



In an attempt to obtain a simpler method of synthesis attention was directed to the preparation by Kimura of symmetrical carbocyanines and neocyanines from quaternary salts of heterocyclic nitrogen bases with α-methyl groups and ethyl trithio-orthoformate in acetic anhydride–pyridine solution (*Chem. Zentr.*, 1937, II, 4187). It appeared possible that, if this reaction proceeded *via* the intermediate formation of the 2-ethylthiovinyl compounds, these might be isolated under appropriate conditions. The formation of a 2-ethylthiovinyl compound was confirmed when 2-methylbenzthiazole methiodide was boiled with ethyl trithio-orthoformate in acetic anhydride. The main product was, however, a trinuclear dye of the neocyanine type as noted by Kimura, but this was contaminated with some of the 2-2′-ethylthiovinylbenzthiazole methiodide. If 2-methylbenzthiazole metho-*p*-toluenesulphonate was used instead of the methiodide, the neocyanine colour, which formed initially on heating, rapidly disappeared and, on addition of potassium iodide solution, the required 2-2′-ethylthiovinylbenzthiazole methiodide was precipitated in good yield substantially free from the neocyanine and carbocyanine.

The reason for the difference in behaviour of the two quaternary salts is puzzling but not without parallel in cyanine dye chemistry. Thus although 2-methyl-β-naphthothiazole ethiodide will not react with ethyl orthoacetate in pyridine (Hamer, *J.*, 1929, 2598), the etho-*p*-toluenesulphonate gives the *meso*-methylcarbocyanine dye under similar conditions (Brooker, B.P. 378,870). The solubility of the quaternary salt is not the sole factor, and the chemistry of the reactions is being investigated further.

By using 2:3:3-trimethylindolenine methiodide the 3:3-dimethyl-2-2′-ethylthiovinylindolenine methiodide was obtained and separated directly, as the cyanine dye formed at the same time was very soluble in acetic anhydride. 2-Ethylthiovinyl derivatives of all the heterocyclic bases employed could be isolated as the alkyl *p*-toluenesulphonates on removal of the acetic anhydride either by hydrolysis or distillation, and the resultant product could be crystallised or precipitated as a less soluble salt by solution in ethanol and addition of an alkali halide solution.

The reaction was effected using other trithio-orthoformate esters such as methyl and benzyl tritho-orthoformate, but the intermediates obtained were less soluble and in the latter case somewhat less reactive. Ten of these reactive intermediates were prepared and converted into carbocyanines in pyridine or ethanol solution with the addition of triethylamine. For direct preparation of carbocyanine dyes it was unnecessary to isolate from the acetic anhydride solution the intermediate which gave the dye on addition of the requisite quaternary salt and triethylamine. Symmetrical carbocyanines were likewise obtained with ease, but since so many have been described previously their preparations have been omitted from the present communication. Two merocyanines were also prepared by condensations with 1-phenyl-3-methyl-5-pyrazolone and *N*-ethylrhodanine in pyridine solution.

Experimental.

Preparation of 2-Alkythiovinyl Compounds.—Ethyl trithio-orthoformate was prepared by the method of Holmberg (*Ber.*, 1907, **40**, 1740).

Quinaldine (14·3 g.) was fused with methyl *p*-toluenesulphonate (18·6 g.) for 1 hour at 100°. The product was dissolved in acetic anhydride (100 c.c.) containing ethyl trithio-orthoformate (22 c.c.) and the solution boiled for 30 minutes. When the original green colour had faded to a dull yellow the acetic anhydride was removed under reduced pressure and the residue crystallised from methanol–ether.

2-2′-Ethylthiovinylquinoline metho-p-toluenesulphonate (12·2 g.) was obtained as yellow needles, m. p. 102° (Found: S, 15·8. $C_{21}H_{23}O_3NS_2$ requires S, 16·0%).

2-2′-Ethylthiovinylbenzthiazole metho-p-toluenesulphonate was prepared similarly from 2-methylbenzthiazole (7·5 g.), methyl *p*-toluenesulphonate (9·3 g.), acetic anhydride (50 c.c.), and ethyl trithio-orthoformate (11 c.c.). The crude product was crystallised from ethanol–ether to give straw-coloured needles, m. p. 171° (decomp.) (Found: S, 24·05. $C_{19}H_{21}O_3NS_3$ requires S, 23·65%).

2-2′-Ethylthio-1′-methylvinylbenzthiazole methiodide was prepared by fusing 2-ethylbenzthiazole (16·3 g.) with methyl *p*-toluenesulphonate (18·6 g.) for 3 hours at 130—140°. The quaternary salt was dissolved in acetic anhydride (100 c.c.) containing ethyl trithio-orthoformate (22 c.c.), and the solution boiled until the colour had faded (30 minutes) and poured into hot potassium iodide solution (100 c.c. of 20%). The dark precipitate was crystallised from methanol to give dark brown crystals (9 g.), m. p. 168° (decomp.) (Found: S, 17·4. $C_{13}H_{16}NIS_2$ requires S, 17%).

2-2′-Ethylthiovinylbenzthiazole methiodide was prepared in a similar way from 2-methylbenzthiazole (14·9 g.), methyl *p*-toluenesulphonate (18·6 g.), acetic anhydride (100 c.c.), and ethyl trithio-orthoformate (22 c.c.). After crystallisation from methanol it was obtained as steel-blue needles (20 g.), m. p. 194° (decomp.) (Found: S, 17·4. $C_{12}H_{14}NIS_2$ requires S, 17·65%).

2-2′-Ethylthiovinylquinoline methiodide was prepared from quinaldine (7·1 g.), methyl *p*-toluenesulphonate (9·3 g.), acetic anhydride (50 c.c.), and ethyl trithio-orthoformate (11 c.c.). The crude product was crystallised from methanol to yield brown crystals (11·3 g.), m. p. 178° (Found: I, 35·4. $C_{14}H_{16}NIS$ requires 35·5%).

2-2′-Ethylthiovinylbenzoxazole methiodide was prepared from 2-methylbenzoxazole (6·6 g.), methyl *p*-toluenesulphonate (9·3 g.), acetic anhydride (40 c.c.), and ethyl trithio-orthoformate (11 c.c.). On pouring into hot potassium iodide solution a tar was first precipitated. After decantation from the tar the aqueous solution was cooled to 0°; a brown solid then crystallised. This was obtained as metallic brown needles from methanol, m. p. 193° (decomp.). A further crop was obtained by basifying the filtrate with sodium carbonate solution. The total yield was 6 g. (Found: S, 9·1. $C_{12}H_{14}ONIS$ requires S, 9·2%).

2-2′-Ethylthiovinylbenzthiazole ethiodide was prepared from 2-methylbenzthiazole (7·5 g.), ethyl *p*-toluenesulphonate (10·0 g.), acetic anhydride (50 c.c.), and ethyl trithio-orthoformate (11 c.c.). It was obtained from methanol as brown crystals (6 g.), m. p. 195° (decomp.) (Found: I, 33·4; S, 16·8. $C_{13}H_{16}NIS_2$ requires I, 33·7; S, 17%).

Benzyl Trithio-orthoformate.—Ethyl formate (9·5 c.c.) was mixed with benzylthiol (28·5 c.c.) and the mixture saturated with hydrogen chloride. The white solid which was deposited (29·7 g., 97%) was collected and dried in a vacuum; m. p. 103°.

2-2′-Benzylthiovinylbenzthiazole methiodide was prepared by fusing 2-methylbenzthiazole (1·49 g.) with methyl *p*-toluenesulphonate (1·86 g.) for 1 hour at 100°; benzyl trithio-orthoformate (4·2 g.) and acetic anhydride (15 c.c.) were added and the mixture boiled for 30 minutes. Acetic anhydride was removed under reduced pressure and the residue dissolved in ethanol (20 c.c.) and poured into aqueous potassium iodide (20 c.c. of a 10% solution). The oily solid precipitate was crystallised from methanol to yield brown crystals (2 g.), m. p. 163° (Found: S, 15·05. $C_{17}H_{16}NIS_2$ requires 15·05%).

Methyl Trithio-orthoformate.—Methylthiol and dry hydrogen chloride were passed simultaneously into ethyl formate (200 c.c.) until saturation occurred. The mixture was then poured on ice and the upper layer separated. The aqueous layer was extracted with ether, and the oil and ether extracts were bulked, washed with sodium carbonate solution and water, and dried (K_2CO_3). The ether was removed and the residue distilled, yielding a colourless oil (50 g.), b. p. 106—108°/10 mm.

2-2′-Methylthiovinylbenzthiazole methiodide was prepared from 2 methylbenzthiazole (3·0 g.), methyl *p*-toluenesulphonate (3·72 g.), acetic anhydride (30 c.c.), and methyl trithio-orthoformate (3·0 c.c.). It was obtained from ethanol as dark brown crystals, m. p. 190° (decomp.) (Found: I, 36·4; S, 18·0. $C_{11}H_{12}NIS_2$ requires I, 36·4; S, 18·4%).

1 : 1′-Diethyl-2 : 4′-carbocyanine Iodide (*[1-Ethyl-2-quinoline][1-ethyl-4-quinoline]trimethincyanine Iodide*).—Quinaldine (1·43 g.) was fused with ethyl *p*-toluenesulphonate (2·00 g.) for 3 hours at 140—150°. The product was dissolved in acetic anhydride (15 c.c.) containing ethyl trithio-orthoformate (2 c.c.), and the solution refluxed for 30 minutes. Lepidine ethiodide (2·98 g.) and triethylamine (1·4 c.c.) were added, and the heating continued for a further 20 minutes; a deep blue colour had then appeared. The green crystals which separated on cooling were collected and crystallised from methanol to yield the *iodide* as grass-green needles, m. p. 255° (Found: I, 26·4. $C_{23}H_{25}N_2I$ requires I, 26·5%).

3 : 3′ : 8-Trimethylthiacarbocyanine Iodide (*Bis-[3-methylbenzthiazole]-α-methyltrimethincyanine Iodide*).—2-Ethylbenzthiazole (1·63 g.) was fused with methyl *p*-toluenesulphonate (1·86 g.) for 1 hour at 100°. 2-2′-Ethylthiovinylbenzthiazole methiodide (2·87 g.) and pyridine (15 c.c.) were added and the mixture refluxed for 15 minutes; a purple colour had then developed. On dilution with water a green *dye* separated; this was collected and crystallised from methanol to yield green crystals with a gold reflex (3·8 g.), m. p. 258° (Found: I, 26·4. $C_{23}H_{23}N_2IS_2$ requires I, 26·6%).

3 : 3′-Diethyloxaselenacarbocyanine Iodide (*[3-Ethylbenzoxazole][3-ethylbenzselenazole]trimethincyanine Iodide*).—2-Methylbenzselenazole (2·00 g.) was fused with ethyl *p*-toluenesulphonate (2·00 g.) for 3 hours at 140—150°. The product was dissolved in acetic anhydride (15 c.c.) containing ethyl trithio-orthoformate (2·2 c.c.) and refluxed for 30 minutes. 2-Methylbenzoxazole ethiodide (2·75 g.) and triethylamine (1·4 c.c.) were added and the heating continued for 15 minutes. The crystals which separated

from the red solution on cooling were collected and crystallised from methanol to yield the *iodide* as deep purple needles with metallic reflex (1·0 g.), m. p. 240° (Found: I, 24·3. $C_{21}H_{21}ON_2ISe$ requires I, 24·2%).

3 : 6′-*Dimethyl*-1′-*ethylthiaquino*-2 : 2′-*carbocyanine iodide* ([3-*methylbenzthiazole*][6-*methyl*-1-*ethyl*-2-*quinoline*]*trimethincyanine iodide*) was prepared similarly from 2-methylbenzthiazole (1·49 g.), methyl *p*-toluenesulphonate (1·86 g.), ethyl trithio-orthoformate (2 c.c.), and *p*-toluquinaldine ethiodide (3·13 g.). It was obtained from methanol as green flaky crystals, m. p. 278° (decomp.) (Found: S, 6·8. $C_{22}H_{27}N_2IS$ requires S, 6·8%).

3′-*Methyl*-3-*ethyloxathiacarbocyanine Iodide* ([3-*Ethylbenzoxazole*][3-*methylbenzthiazole*]*trimethincyanine Iodide*).—2-Methylbenzthiazole (1·49 g.) and methyl *p*-toluenesulphonate (1·86 g.) were heated at 100° for 1 hour. The product was dissolved in acetic anhydride (15 c.c.) containing ethyl trithio-orthoformate (2 c.c.) and refluxed for 30 minutes. 2-Methylbenzoxazole ethiodide (2·89 g.) and triethylamine (1·4 c.c.) were added and the heating continued for 20 minutes. The pink solution was diluted with ethanol and the precipitated red crystals were collected and crystallised from methanol to yield the *iodide* as purple crystals, m. p. 242° (decomp.) (Found: I, 27·0; S, 6·9. $C_{20}H_{19}ON_2IS$ requires I, 27·4; S, 6·9%).

3 : 3′-*Diethyloxathiacarbocyanine iodide* ([3-*ethylbenzoxazole*][3-*ethylbenzthiazole*]*trimethincyanine iodide*) was prepared similarly from 2-methylbenzoxazole (4·0 g.), ethyl *p*-toluenesulphonate (6·0 g.), ethyl trithio-orthoformate (6 c.c.), and 2 methylbenzthiazole ethiodide (9·0 g.). It was obtained as dark blue needles, m. p. 243° (decomp.) (Found: I, 26·7. $C_{21}H_{21}ON_2IS$ requires I, 26·8%).

3 : 3′-*Dimethyloxathiacarbocyanine Iodide* ([3-*Methylbenzoxazole*][3-*methylbenzthiazole*]*trimethincyanine Iodide*).—2-Methylbenzoxazole methiodide (5·3 g.) and 2-2′-ethylthiovinylbenzthiazole methiodide (7·26 g.) were refluxed in pyridine (40 c.c.) for 1 hour. The *dye* which separated on dilution with water was collected and crystallised from methanol to yield 5·2 g. of fluffy red needles, m. p. 254° (decomp.) (Found: I, 28·0. $C_{19}H_{17}ON_2IS$ requires I, 28·3%).

3 : 3′-*Dimethylthiathiazolinocarbocyanine Iodide* ([3-*Methylthiazoline*][3-*methylbenzthiazole*]*trimethincyanine Iodide*).—2-Methylthiazoline (1·00 g.) was fused with methyl *p*-toluenesulphonate (1·86 g.) for 1 hour at 100°. The product was dissolved in acetic anhydride (10 c.c.) and ethyl trithio-orthoformate (2·2 c.c.), and the mixture refluxed for 30 minutes. 2-Methylbenzthiazole methiodide (2·85 g.) and triethylamine (1·4 c.c.) were added and the mixture refluxed for 10 minutes; a thick precipitate had then formed. The *dye* was filtered off and crystallised from methanol to yield dark red crystals with a bright green reflex (1·5 g.), m. p. 278° (decomp.) (Found: I, 30·3. $C_{15}H_{17}N_2IS_2$ requires I, 30·5%).

1-*Phenyl*-3 : 1′ : 3′ : 3′-*tetramethyl*-2′-*ethylideneindolylidene*-5-*pyrazolone*.—1-Phenyl-3-methyl-5-pyrazolone (1·74 g.) and 1 : 3 : 3-trimethyl-2-2′-ethylthiovinylindolenium iodide (3·73 g.) were dissolved in dry pyridine (25 c.c.) and the mixture boiled for 15 minutes. The *dye* precipitated on dilution with water was collected and crystallised from methanol to yield red needles (2·9 g.), m. p. 183° (Found: C, 77·3; H, 6·3. $C_{23}H_{23}ON_3$ requires C, 77·2; H, 6·4%).

2-*Keto*-4-*thio*-3′-*methyl*-3-*ethyl*-5 : 2′-*ethylidenebenzthiazolylidenetetrahydrothiazole* was prepared similarly from *N*-ethylrhodanic acid (0·8 g.), 2-2′-ethylthiovinylbenzthiazole methiodide (1·81 g.), and pyridine (10 c.c.). It was obtained from methanol as red needles, m. p. 280° (Found: C, 54·2; H, 4·0; S, 29·0. $C_{15}H_{14}ON_2S_3$ requires C, 53·9; H, 4·2; S, 28·75%).

The authors wish to thank the Directors of Ilford Limited for permission to publish this work, Mr. F. P. Doyle for the preparation of some of the 2-ethylvinyl compounds, and Mr. A. J. Axford for the analytical results.

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ILFORD LIMITED, ILFORD.

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137. *Preparation of Symmetrical and Unsymmetrical Neocyanines: Structure of the Neocyanines.*

By J. D. KENDALL and J. R. MAJER.

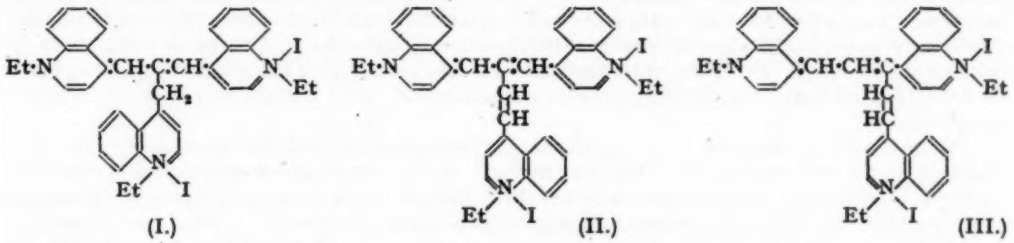
Carbocyanine dyes have been condensed with heterocyclic quaternary salts containing reactive methyl groups and esters of trithio-orthoformic acid in acetic anhydride solution to yield trinuclear dyes of the neocyanine type. By this method, unsymmetrical neocyanines containing two and three different heterocyclic rings have been prepared. The experimental evidence obtained supports the formula for neocyanines originally suggested by König.

THREE different formulæ have been proposed for the neocyanines. Hamer (*J.*, 1928, 1472) assigned to the neocyanine obtained from lepidine ethiodide the formula (I).

Later, Brooker, Hamer, and Mees replaced this by formula (II) in which the three heterocyclic nuclei were connected by a conjugated chain passing through the *meso*-carbon atom of the trimethin chain (*J. Opt. Soc. Amer.*, 1933, **23**, 216).

König (*Z. wiss. Phot.*, 1935, **34**, 15), without giving any reasons, suggested a third formula (III) in which the heterocyclic nuclei are connected by a conjugated chain passing through one of the terminal carbon atoms of the trimethin chain. The dye in this case may be regarded as a

substituted carbocyanine or a dicarbocyanine in which the following formula represents one of the extremes of the resonance hybrids.



(I.) (II.) (III.)

This formula received immediate support from Kendall (*Proc. Ninth Int. Congress of Phot., Paris*, 1935, 248), mainly from considerations of the photographic properties of the neocyanines, and from Hamer (*Chem. and Ind.*, 1935, **13**, 640) as a " formula, according to which a reasonable picture of the mechanism of formation of the dye is obvious ".

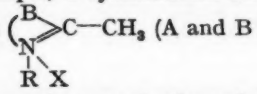
Theoretical considerations of the chemistry of the neocyanines likewise favour the König formula. If as is possible, the dinuclear carbocyanine is intermediate in the formation of the trinuclear neocyanine, a dye of structure (II) must arise by a reaction involving the hydrogen atom on the *meso*-carbon atom of the trimethin chain. In the quinoline series, however, only hydrogen atoms linked to carbon atoms directly attached to the carbon in the α-position, or the vinylogous γ-position, to the nitrogen atom are readily reactive. The position of the *meso*-methin group of the trimethin chain corresponds vinylogously to that of a β-methyl group, and the hydrogen atoms of β-methylquinolines are notably unreactive. The terminal methin groups on the other hand correspond to the methyl groups of lepidine and therefore possess hydrogen atoms known to be reactive. Any reaction on a hydrogen atom of a carbocyanine dye may therefore be expected to involve one of the terminal methin groups rather than the *meso*-methin. Experimental evidence detailed below supports both the formation of the neocyanine type of dye *via* the carbocyanine, and the König formula opposed to formula (II).

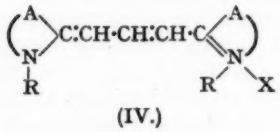
Since the reactants required for the synthesis of both the carbocyanine and a neocyanine are a quaternary salt containing a reactive methyl group and a formic acid derivative such as ethyl orthoformate, iodoform, or ethyl trithio-orthoformate, it would appear that, provided the carbocyanine is intermediate in the formation of the neocyanine, the latter should be obtainable from the former by further condensation with the original reactants under appropriate conditions. Consideration of the analytical figures shows that the molecule of a neocyanine contains two acid radicals, whilst a molecule of a carbocyanine contains only one. In the conversion of a carbocyanine into a neocyanine it would therefore appear preferable that the additional heterocyclic nucleus should be in the form of a quaternary salt. Conditions which favour the formation of an *N*-alkylmethylene base would be expected to be unfavourable to neocyanine formation. This explains the superiority of Kimura's method in which acetic anhydride is used as a solvent rather than pyridine, since the presence of a basic solvent would tend to favour conversion of the quaternary salt into the methylene base. It explains likewise why Hamer found that improved yields of neocyanine, as compared with those of kryptocyanine, are obtained by reducing the quantities of pyridine employed for solvent purposes.

On the basis of these assumptions an attempt was first made to prepare the neocyanines by interaction of the quaternary salts of α-ω-ethylthiovinyl heterocyclic bases with carbocyanines in acetic anhydride, but the reactions failed to give the required dyes. This appeared inexplicable unless the formation of the neocyanine proceeded *via* a primary condensation product of the trithio-orthoformate and the carbocyanine. A solution of 3 : 3-diethylthiacarbocyanine iodide in acetic anhydride was therefore refluxed with ethyl trithio-orthoformate and 2-methylbenzthiazole methiodide; the colour deepened gradually from magenta to blue, whilst a green dye separated from solution. Analysis and the properties of this dye showed it to be the anticipated neocyanine. A neocyanine dye was obtained similarly by using *p*-toluquinaldine methiodide instead of 2-methylbenzthiazole methiodide. Reactions with 2 : 3 : 3-trimethylindolenine methiodide and 2 : 3 : 3 : 6-tetramethylindolenine methiodide were also attempted, but these were found to be much less reactive than the thiazole quaternary salts and the resulting neocyanines were more soluble and difficult to isolate.

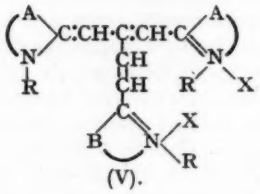
The ability to give neocyanines did not appear to be limited to the quaternary iodides of the carbocyanines, and 3 : 3′-diethylthiacarbocyanine *p*-toluenesulphonate was condensed with

ethyl trithio-orthoformate and both 2-methylbenzthiazole etho-*p*-toluenesulphonate and 2-methylbenzselenazole metho-*p*-toluenesulphonate, the resulting dyes being converted into the di-iodides with potassium iodide solution. 1 : 3 : 3 : 1′ : 3′ : 3′-Hexamethylindocarbocyanine iodide was very unreactive and only appeared to condense to a slight extent with very insoluble quaternary salts, but 3 : 3′-diethylselenacarbocyanine iodide appeared to be as reactive as its sulphur analogue. 3 : 3′-Diethyloxacarbocyanine iodide readily gave the symmetrical neocyanine on being heated with 2-methylbenzoxazole ethiodide and ethyl trithio-orthoformate in acetic anhydride.

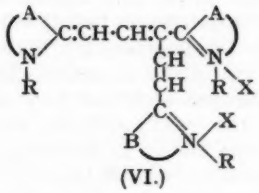
The neocyanines derived from a symmetrical carbocyanine and the quaternary salts of a different ring system contain two dissimilar nuclei. By the use of unsymmetrical carbocyanines, however, neocyanines which contained two or three different nuclei could be prepared. Attempts at formulation of these neocyanines indicated that a study of a simple series of unsymmetrical dyes might serve to demonstrate the correctness or otherwise of the König formula. If, for example, a symmetrical carbocyanine (IV) is converted into a neocyanine with a quaternary salt  (A and B being the remainder of dissimilar heterocyclic nuclei) the resulting neocyanine may be formulated as either (V) or (VI) (resonance extremes), depending whether reaction occurs at the *meso* or terminal methin group.



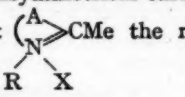
(IV.)

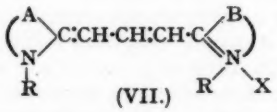


(V).

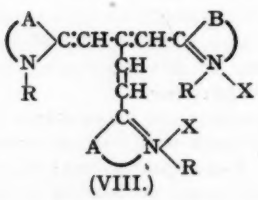


(VI.)

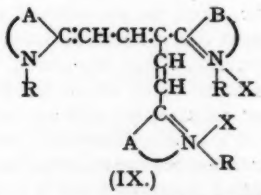
If instead of the symmetrical carbocyanine, the unsymmetrical carbocyanine (VII) is converted into a neocyanine with the quaternary salt  the resulting dye may be represented as either (VIII), (IX), or (X) (resonance extremes) :



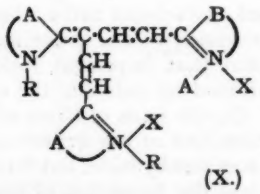
(VII.)



(VIII.)



(IX.)



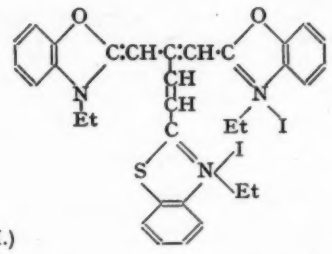
(X.)

Isomers on König formulation.

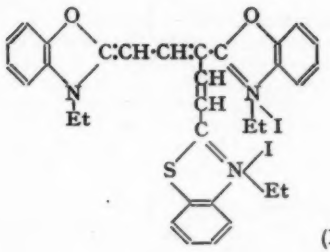
From these it is obvious that under no conditions can the neocyanines obtained be identical on the basis of formulæ (V) and (VIII), whilst formula (VI) is identical with (X) (two extremes of the resonance hybrid). In the event, therefore, of the dyes prepared by the two different methods being identical, the formula representing a neocyanine as a carbocyanine substituted in the *meso*-methin group must be incorrect.

When 3 : 3′-diethyloxathiacarbocyanine iodide was heated in acetic anhydride with 2-methylbenzoxazole ethiodide and ethyl trithio-orthoformate, only one product was obtained which was identical in all respects with the neocyanine produced from 3 : 3′-diethyloxacarbocyanine iodide and 2-methylbenzthiazole ethiodide. It follows, therefore, that the formula of the

compound produced cannot be (XI) but may be a hybrid of which (XII) represents one of the resonance extremes.

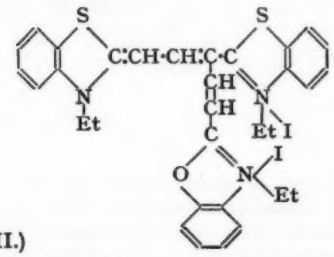


(XI.)

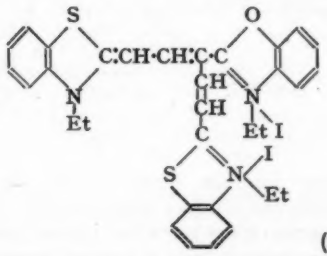


(XII.)

The condensation of 3 : 3′-diethyloxathiacarbocyanine iodide and 2-methylbenzthiazole ethiodide also gave only one neocyanine, but this was different from that obtained from 3 : 3′-diethylthiacarbocyanine iodide and 2-methylbenzoxazole ethiodide. It is suggested, therefore, that whilst the structure of the latter may be represented as (XIII) that of the former is (XIV).

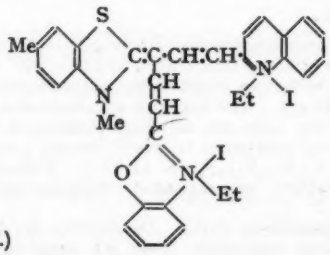


(XIII.)

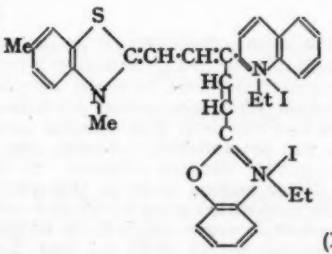


(XIV.)

3 : 6-Dimethyl-1′-ethyl-2 : 2′-thiaquinocarbocyanine iodide on conversion into the neocyanine with 2-methylbenzoxazole ethiodide likewise gave only one product which may be represented as either (XV) or (XVI). The predominant formation of only one neocyanine from an unsymmetrical carbocyanine is remarkable. It is explicable, however, if the electronic displacements in the unsymmetrical molecule under conditions of reaction are such as to induce a high reactivity on only one of the terminal methin groups. If this is correct the type of neocyanine formed is always determined by the carbocyanine employed and not by the quaternary salt with the reactive methyl group.

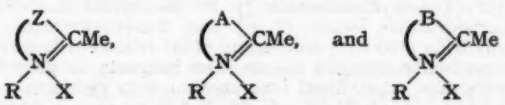


(XV.)



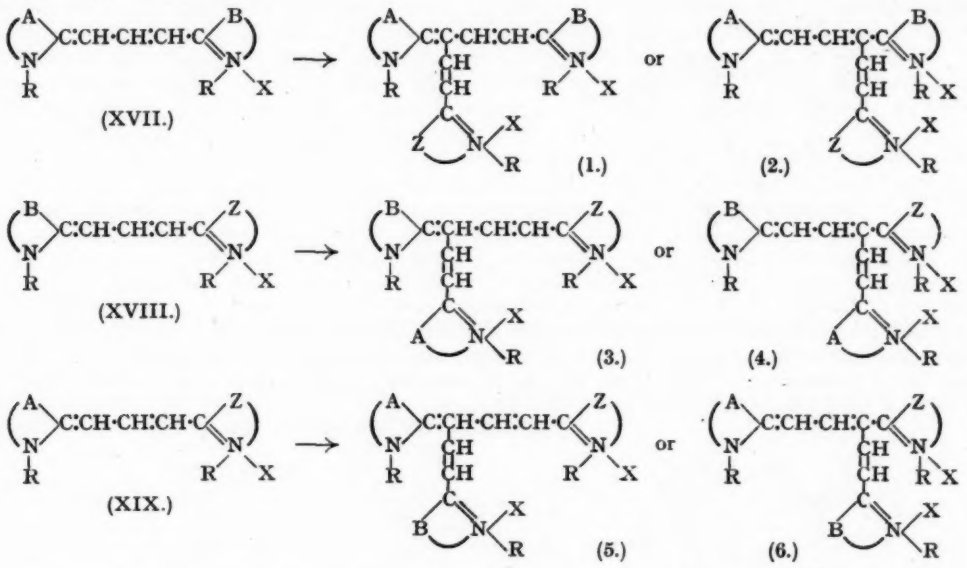
(XVI.)

The precise formulation of a neocyanine with three different heterocyclic nuclei may be possible, however, by a simple permutation of the nuclei in the reactants. If three different unsymmetrical carbocyanines (XVII), (XVIII), and (XIX) are converted into neocyanines



containing three dissimilar heterocyclic nuclei by condensation with quaternary salts of the three heterocyclic bases respectively (where Z, A, and B represent the remainder of heterocyclic

rings), the resulting dyes should have structures corresponding to the following formulæ (1) or (2), (3) or (4), and (5) or (6).



In these formulæ, however, the pairs (1) and (5), (2) and (3), and (4) and (6) are identical. If, therefore, the product from the first of these reactions is identical with that from the second, the neocyanine must be of the type of formula (2). Similarly, if the product from the reaction is identical with that from the third reaction its formula would be (1). Again, if the products of the second and third reactions are identical the formula would be (4). Only in the event of all three reaction products being different would it not be possible to decide the structure by this method. It is hoped later to communicate the results of investigations on a series of unsymmetrical neocyanines prepared according to this scheme.

Attempts to convert other cyanine dyes, for example, monomethin cyanines, pinaflavols, and tricarbocyanines, into trinuclear dyes appeared to be unsuccessful. There were indications, however, that dicarbocyanines might be converted to trinuclear dyes by the method used for the preparation of neocyanines from carbocyanines.

Experimental.

[*Bis*-2-(3-*ethylbenzthiazole*)][γ-2′-(3-*ethylbenzthiazole*)]*pentamethincyanine Di-iodide.**—A mixture of 2-methylbenzthiazole (0·4 g.) and ethyl *p*-toluenesulphonate (0·55 g.) was heated at 140—150° for 4 hours, and the product dissolved in acetic anhydride (50 c.c.) containing ethyl trithio-orthoformate (0·5 g.) and 3 : 3′-diethylthiacarbocyanine *p*-toluenesulphonate (1·45 g.). The mixture was heated under reflux for 1 hour and the deep blue solution poured, with stirring, into hot aqueous potassium iodide. A green dye was precipitated, collected, and crystallised from methanol to yield bronze green crystals (0·6 g.), m. p. 241° (decomp.) (Found : S, 12·01. Calc. for $C_{32}H_{31}N_3I_2S_3$: S, 11·9%). Kimura (*loc. cit.*) gives the decomposition point of this neocyanine as 260—261°, but repeated crystallisation failed to raise the decomposition point of the dye obtained above.

[*Bis*-2-(3-*ethylbenzoxazole*)][γ-2′-(3-*ethylbenzoxazole*)]*pentamethincyanine Di-iodide.*—3 : 3′-Diethyloxacarbocyanine iodide (0·88 g.) and 2-methylbenzoxazole ethiodide (0·64 g.) were dissolved by heating in acetic anhydride (30 c.c.) containing ethyl trithio-orthoformate (0·4 c.c.), and the mixture boiled under reflux for 30 minutes. The solution, which was originally orange, became deep red, and on cooling small green crystals separated. The dye was collected and crystallised from methanol to yield minute green crystals with a golden reflex (0·48 g.), m. p. 233° (decomp.). Kimura (*loc. cit.*) gives m. p. 225° (decomp.) (Found : I, 33·7. Calc. for $C_{32}H_{31}O_2N_3I_2$: I, 33·46%).

[2-(3-*Ethylbenzthiazole*)][2′-(3-*methylbenzthiazole*)][γ-2″-(3-*ethylbenzthiazole*)]*pentamethincyanin Di-iodide.*—3 : 3′-Diethylthiacarbocyanine iodide (2 g.) and 2-methylbenzthiazole methiodide (1·2 g.) were dissolved in acetic anhydride (100 c.c.) containing ethyl trithio-orthoformate (0·8 g.) and refluxed for 1 hour. The solution gradually changed colour from magenta to deep blue, and a green powder separated. This was collected and crystallised from methanol to yield the *dye* as vivid green crystals (2·3 g.), m. p. 220° (decomp.) (Found : I, 31·75. $C_{31}H_{29}N_3I_2S_3$ requires I, 32·0%).

* Hamer, Rathbone, and Winton (*J.*, 1947, 1434) named the neocyanines as derivatives of trimethincyanine. The present authors prefer to consider them as substituted pentamethincyanines.

[2-(3-*Ethylbenzthiazole*)][2′-(1 : 6-*dimethylquinoline*)][γ-2″-3-*ethylbenzthiazole*)]*pentamethincyanine Di-iodide*.—3 : 3′-Diethylthiacarbocyanine iodide (2·5 g.) and *p*-toluquinaldine methiodide (1·5 g.) were dissolved in acetic anhydride (100 c.c.) containing ethyl trithio-orthoformate (0·8 g.) and the solution refluxed for 2 hours; it had then become deep blue. The green powder which separated was collected and extracted with 5 × 10 c.c. portions of methanol. The *dye* crystallising from the methanol was collected and the process repeated. The fractions were finally bulked and recrystallised to yield dark green crystals with a bronze lustre (2·5 g.), m. p. 221° (Found : I, 31·7. $C_{34}H_{33}N_3I_2S_2$ requires I, 31·6%).

[2-(3-*Ethylbenzselenazole*)][2′-(1-*ethylquinoline*)][γ-2″-(3-*ethylbenzselenazole*)]*pentamethincyanine Di-iodide*.—3 : 3′-Diethylselenacarbocyanine iodide (1·5 g.) and quinaldine ethiodide (1 g.) were dissolved in acetic anhydride (50 c.c.) containing ethyl trithio-orthoformate (0·6 g.) and refluxed for 2 hours. The *dye* which separated from the blue solution on cooling was collected and crystallised from methanol to yield metallic green needles (0·5 g.), m. p. 218° (Found : N, 4·9; I, 28·2. $C_{34}H_{33}N_3I_2Se_2$ requires N, 5·2; I, 28·4%).

[2-(3-*Ethylbenzthiazole*)][2′-(3-*methylbenzselenazole*)][γ-2″-(3-*ethylbenzthiazole*]*pentamethincyanine Di-iodide*).—2-Methylbenzselenazole (1·0 g.) and methyl *p*-toluenesulphonate (0·93 g.) were heated at 120° for 3 hours. The product was dissolved in acetic anhydride (100 c.c.) containing ethyl trithio-orthoformate (0·8 g.) and 3 : 3-diethylthiacarbocyanine *p*-toluenesulphonate (2·6 g.). The solution was refluxed for 2 hours, poured into boiling aqueous potassium iodide solution, and the green *dye* precipitated was crystallised from ethanol to give green needles (2 g.), m. p. 225° (Found : I, 30·05. $C_{31}H_{29}N_3I_2S_2Se$ requires I, 30·2%).

[2-(3-*Ethylbenzthiazole*)][2′-(3-*ethylbenzoxazole*)][γ-2″-(3-*ethylbenzthiazole*)]*pentamethincyanine Di-iodide*.—3 : 3′-Diethylthiacarbocyanine iodide (2·5 g.) and 2-methylbenzoxazole ethiodide (1·5 g.) were dissolved by boiling in acetic anhydride (100 c.c.) containing ethyl trithio-orthoformate (0·8 g.). The solution was refluxed for 2 hours; the magenta colour had then changed to a deep purple, and a green solid had separated; this was crystallised from methanol to yield the *dye* as grass-green needles (2 g.), m. p. 222° (Found : I, 32·3. $C_{32}H_{31}ON_3I_2S_2$ requires I, 32·1%).

[*Bis*-2-(3-*ethylbenzthiazole*)][γ-2′-(3-*ethylbenzoxazole*)]*pentamethincyanine Di-iodide*.—3 : 3′-Diethyloxathiacarbocyanine iodide (2·4 g.) and 2-methylbenzthiazole ethiodide (1·5 g.) were dissolved in acetic anhydride (50 c.c.) containing ethyl trithio-orthoformate (0·8 c.c.) and the solution was refluxed for 2 hours; it had then become deep purple and had deposited a green *dye*. This was crystallised from methanol to yield brownish-green needles (1·4 g.), m. p. 235° (Found : I, 32·05. $C_{32}H_{31}ON_3I_2S_2$ requires I, 32·1%).

[2-(3-*Ethylbenzoxazole*)][2′-(3-*ethylbenzthiazole*)][γ-2″-(3-*ethylbenzoxazole*)]*pentamethincyanine Di-iodide*.—3 : 3-Diethyloxathiacarbocyanine iodide (2·4 g.) and 2-methylbenzoxazole ethiodide (1·45 g.) were dissolved in acetic anhydride (15 c.c.) containing ethyl trithio-orthoformate (0·8 g.), and the solution refluxed for 30 minutes. Ethanol (15 c.c.) was added and then ether until a faint cloudiness appeared. The *dye*, which crystallised on cooling, was recrystallised from methanol to yield dark green octahedra (2 g.), m. p. 190° (decomp.) (Found : I, 32·7. $C_{32}H_{31}O_2N_3I_2S$ requires I, 32·75%). The dye was obtained similarly from 3 : 3′-diethyloxacarbocyanine iodide (2·5 g.) and 2-methylbenzthiazole ethiodide (1·5 g.) as dark green octahedra, m. p. 190° (decomp.) (Found : I, 32·8%). Both samples gave identical optical sensitizing in silver iodobromide emulsions, extending the normal sensitivity to *ca.* 6800 A. with a shallow maximum at *ca.* 6400 A. The absorption curves of both samples in ethanol were likewise identical, with sharp maxima at 6100 A.

[2-(3-*Ethylbenzoxazole*)][2′-(6-*methyl*-1-*ethylquinoline*)][γ-2″-(3-*methylbenzthiazole*)]*pentamethincyanine Di-iodide* (*or Isomer*).—This was prepared likewise from 3 : 6′-dimethyl-1′-ethylthiaquinocarbocyanine iodide (1·5 g.), 2-methylbenzoxazole methiodide (0·7 g.), and ethyl trithio-orthoformate (0·4 g.). It was obtained as brown needles, m. p. 237° (decomp.) (Found : I, 33·0. $C_{33}H_{31}ON_3I_2S$ requires I, 32·9%).

The authors are indebted to the Directors of Ilford Limited for permission to publish this work, and to Mr. A. J. Axford for the analytical results.

RODENSIDE ORGANIC LABORATORY,
ILFORD LIMITED, ILFORD.

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138. *Esters containing Phosphorus. Part IV. Diisopropyl Fluorophosphonate.*

By B. C. SAUNDERS and G. J. STACEY.

The preparation of *diisopropyl fluorophosphonate* from the chlorophosphonate is described. An account is given of the preparation of the fluorophosphonate from diisopropyl hydrogen phosphite by a " one-stage " process which forms the basis of the large-scale preparation of the compound. The chemical and physiological properties of this and of certain related compounds are described.

DURING the late war investigations were carried out at Cambridge on toxic fluorophosphonates and related compounds for the Ministry of Supply, and reports were submitted to the Ministry and were also made available to American workers. Brief preliminary accounts of some aspects of the work have recently been published (McCombie and Saunders, *Nature*, 1946, **157**, 287, 776). During the years 1941—1945, we prepared a large number of compounds of different types

containing the >POF group. Many of these were highly toxic by inhalation and injection, and possessed powerful miotic action (constriction of the pupils of the eyes) at very low concentrations. The more toxic compounds possessed intense anti-choline-esterase activity.

Until this work began practically nothing was known about the preparation or properties of fluorophosphonic esters. Only two had been reported, *viz.*, the dimethyl and the diethyl ester (Lange and Krüger, *Ber.*, 1932, **65**, 1598). The method of preparation was very tedious and laborious, and yields were so low as to render the method impracticable. In Part I (McCombie, Saunders, and Stacey, *J.*, 1945, 380) was described the preparation of dialkyl hydrogen phosphites (I) in 90% yield from phosphorus trichloride and the appropriate alcohol, the merit of the method being that no tertiary base was necessary to remove the hydrogen chloride produced. It was recorded that chlorine readily converted the dialkyl hydrogen phosphites into the dialkyl chlorophosphonates (II) in high yield.

The present paper describes the conversion of dialkyl chlorophosphonates into the corresponding fluorophosphonates in excellent yield by means of sodium fluoride. (Fluorination could also be effected by means of silver fluoride, zinc fluoride, or antimony trifluoride, but with the last two reagents complexes of the fluorophosphonate and the inorganic salt were formed.)

$$PCl_3 + 3HOR \longrightarrow P(OR)_3 \xrightarrow[\text{stage I}]{} P(OH)(OR)_2 \rightleftharpoons O{:}PH(OR)_2$$

(I.)

$$\xrightarrow[\text{stage II}]{Cl_2} O{:}PCl(OR)_2 \xrightarrow[\text{stage III}]{NaF} O{:}PF(OR)_2$$

(II.) (III.)

The above reactions are of very general application, and the present series of papers will describe the preparation and properties of numerous compounds of type (III) in which R is varied. The present paper is confined mainly to a discussion of *diisopropyl fluorophosphonate* (R = Pr$^{\beta}$). This compound was first described in 1941 (Saunders, Ministry of Supply Meeting, London, Dec. 11th, 1941; McCombie and Saunders, Report to Ministry of Supply, Dec. 18th, 1941). As shown below, it proved to be of great importance, and because of its remarkable physiological properties a study was made of its preparation on a technical scale. Using carbon tetrachloride as solvent, *iso*propyl alcohol was converted into pure di*iso*propyl hydrogen phosphite (stage I) in 89% yield. Without a solvent the yield was 86·4%. Chlorination of the hydrogen phosphite gave 76% of pure di*iso*propyl chlorophosphonate (stage II). (Yields of 80—90% of slightly less pure chlorophosphonate could, however, be easily obtained.) By heating the chlorophosphonate, dissolved in dry benzene, with dry sodium fluoride (stage III), pure di*iso*propyl fluorophosphonate was obtained in 90% yield. Thus the fluorophosphonate was obtainable in a pure condition by a three-stage process from phosphorus trichloride and *iso*propyl alcohol, and the overall yield was *ca.* 60—70%. The compound so obtained was identical with that obtained by heating an authentic specimen of dry silver fluorophosphonate with *iso*propyl iodide. In the ethyl series the yields of the products at stages I, II, and III were 93%, 87%, and 91% respectively.

The individual stages having been established, the whole process was then re-examined with a view to preparing di*iso*propyl fluorophosphonate on a technical scale. As a result of many experiments it was found that the process could be run virtually as a " one-stage " process by adding phosphorus trichloride to *iso*propyl alcohol dissolved in carbon tetrachloride, without external cooling. The hydrogen phosphite was not isolated, but the crude product (still in carbon tetrachloride) was chlorinated, and the solution of crude chlorophosphonate thus obtained was heated with sodium fluoride. After filtration and removal of carbon tetrachloride, the residue was distilled giving pure di*iso*propyl fluorophosphonate. The overall yield was *ca.* 75%. The process was patented (B.P., Ministry of Supply, McCombie and Saunders, Sept. 15th, 1943).

An important feature of the above process was that it could be carried out in an all-glass apparatus as no fluorine or hydrogen fluoride was produced. In arriving at this " one-stage " process other useful modifications were worked through. (Details appear in Reports on Fluorophosphonates to the Ministry of Supply Nos. 3 to 8, Feb. 27th, 1942, to March 1st, 1943.)

Di*iso*propyl fluorophosphonate is a practically odourless, mobile liquid, b. p. 183°/760 mm. (by extrapolation), f. p. *ca.* −82°. This wide range of temperature over which the compound is liquid adds to the usefulness. A specimen of the pure liquid has remained unchanged in a glass vessel for several years. Whereas the chlorophosphonate was readily hydrolysed by water, hydrolysis of the fluorophosphonate was slow and took 72 hours for completion

at 15° and then only in the presence of a large excess of water (1% solution; solubility, 1·5%): $P(OPr^{\beta})_2 \cdot OF + H_2O = P(OPr^{\beta})_2 \cdot OH + HF$. Dimethyl and diethyl fluorophosphonate were hydrolysed much more quickly, the order being Me > Et > Pr^{β}; complete hydrolysis of the ethyl ester took about 4 hours. The di*iso*propyl, but not the diethyl, ester could be steam-distilled. Di*iso*propyl fluorophosphonate did not, like the chlorophosphonate, give the anilinophosphonate on treatment with aniline.

These dialkyl fluorophosphonates were readily hydrolysed by dilute sodium hydroxide solution according to the equation: $O{:}PF(OR)_2 + 2NaOH = O{:}P(ONa)(OR)_2 + NaF + H_2O$.

On Dec. 11th, 1941, one of us (B. C. S.) reported at a Ministry of Supply Meeting in London the highly toxic nature of di*iso*propyl fluorophosphonate as a lethal inhalant. The quick "knock-out" action of the compound was stated to be comparable with that produced by hydrogen cyanide. Another remarkable effect at much lower, and non-fatal, concentrations was stressed at the time. An intense constriction of the pupils of the eyes took place (miotic effect). Subsequently intensive work was carried out, and the results may be summarised as follows:

(1) *Toxicity by inhalation.** Batches of animals (rabbits, guinea-pigs, rats, and mice) were exposed in a 1·78 m.³ chamber for 10 minutes. A concentration of the ester of 1 in 10,000 killed 18/23 of the animals, all the deaths taking place within 25 minutes of the beginning of the exposure. The dimethyl ester killed 14/23 and the diethyl ester 11/23 at this concentration. More precise experiments showed that the L.C. 50 for di*iso*propyl fluorophosphonate for 10-minute exposures (deaths within 2 hours) was 0·44 mg./l. for mice and 0·36 mg./l. for rats. This means that the compound is more toxic than carbonyl chloride, cyanogen chloride, or chloropicrin. For exposures of less than about 13 minutes the compound is slightly less toxic, and for exposures longer than 13 minutes more toxic, than hydrogen cyanide. The symptoms were salivation, muscular weakness, gasping, and finally cessation of respiration.

(2) *Miotic effect.* The various dialkyl fluorophosphonates were tested on the persons mentioned at the end of the paper. Members of the team entered a 10 m.³ chamber containing a concentration of 1 in 1,000,000 (*i.e.*, 0·0082 mg./l.) of the *iso*propyl compound for 5 minutes. Practically nothing was observed until some 5 minutes after leaving the chamber; severe miosis then set in. This often persisted for as long as 7 days, and there was usually no sign of relaxation until after 72 hours. The eye effects may be summarised as follows:

(*a*) Pupil constriction. All subjects affected. The amount of light entering the eye was greatly reduced, and "darkness" set in. The incapacitation was worse in a poor light (*e.g.*, at twilight).

(*b*) Visual acuity affected. Varied from individual to individual.

(*c*) Powers of accommodation affected. The younger subjects usually suffered most.

(*d*) Photophobia and headaches almost always accompanied the miosis. Pain was experienced when changing from a bright to a dull light.

(*e*) Congestive iritis was caused by rather higher concentrations than the above, *e.g.*, at 0·05 mg./l. for 5 minutes.

Apart from controlled experiments such as the above, we repeatedly found when working with the compound that amounts undetectable chemically caused miosis, even when protective measures were taken. Minute traces of the vapour adhering to clothing could produce significant miosis. We observed, as early as 1941, that the dimethyl and the diethyl ester produced far less intense miosis than that caused by the di*iso*propyl ester. The effect of the dimethyl compound usually wore off in a matter of hours, whereas that of the ethyl compound usually lasted about 2 days.

(3) *Toxicity by injection.*† For intravenous injection into rabbits the L.D. 50 of di*iso*propyl fluorophosphonate in normal saline was *ca.* 0·5 mg./kg. Pupil-constriction began 2 minutes after injection, followed by loss of muscular co-ordination and then by respiratory collapse. For subcutaneous injection into mice the figure was higher at approximately 4·0 mg./kg.

(4) *Anti-choline-esterase activity.* The dialkyl fluorophosphonates have been shown to be powerful inhibitors of the enzyme choline-esterase. Here again the order was Pr^{β} > Et > Me. M. Dixon (Report to Ministry of Supply, 1942) showed that our specimens of the di*iso*propyl ester were effective in concentrations as low as 10^{-10}M, and were therefore much more powerful than eserine. On the other hand, sodium fluoride and ammonium fluorophosphonate required

* Toxicity by inhalation (L.C. 50) is expressed as the concentration in mg. per l. required to kill 50% of the animals exposed.

† Toxicity by injection is expressed as the dose in mg. per kg. body weight required to kill 50% of the animals treated.

concentrations of 10^{-3}M to produce 50% inhibition in the standard test. W. Feldberg (Report to Ministry of Supply, Nov., 1942), using a different technique with these same samples, also showed that the di*iso*propyl ester was much more potent than eserine towards choline-esterase.

Mixtures.—The freezing points of mixtures of 2 : 2′-dichlorodiethyl sulphide (H) and di*iso*propyl fluorophosphonate were determined, measured volumes of the liquids of known densities being used, and great accuracy is not claimed. A mixture of 60% of H and 40% of the ester melted at *ca.* 0°, and a mixture containing 90% of the ester melted as low as −38°.

Other Uses.—In two British Patents (above, and also April 17th, 1944) it has been claimed that some of these toxic compounds might be useful as insecticides, fungicides, bactericides, and disinfectants, and that they might be capable of general clinical application. Such claims are now being realised, particularly in connexion with myasthenia gravis, glaucoma, and paralytic ileus.*

Experimental.

*Di*iso*propyl Fluorophosphonate.*—Di*iso*propyl chlorophosphonate (298 g.) was dissolved in dry benzene (150 c.c.) and gently heated with dry finely powdered sodium fluoride (140 g.) in a flask fitted with a reflux condenser and mechanical stirrer. The temperature was adjusted so that the benzene solution was kept gently boiling, vigorous stirring being maintained. After 3½ hours a small quantity of kieselguhr was added, and the mixture shaken and filtered. The benzene was distilled off (and used for subsequent runs) and the *ester* distilled at 73°/16 mm. Yield, 246 g. (90%) (Found : F, 10·32. $C_6H_{14}O_3FP$ requires F, 10·32%). The determination of fluorine in this and related compounds was carried out by a special technique to ensure non-interference by phosphorus. The procedure employed throughout this work was due to Chapman, Heap, and Saunders, and full details will appear elsewhere.

Hydrolysis by N/2*-sodium hydroxide.* Di*iso*propyl fluorophosphonate (2·224 g.) was heated gently under reflux with 100 ml. of 0·49N-sodium hydroxide for 30 minutes; back titration of an aliquot by 0·5N-sulphuric acid (phenolphthalein as indicator) showed that 1 mol. of the fluorophosphonate required 1·94 mols. of sodium hydroxide. Now 4 mols. are required to effect complete hydrolysis to sodium orthophosphate according to equation (1), but only 2 mols. are required either for the removal of fluorine alone and conversion into sodium di*iso*propyl phosphate (2) or for conversion into disodium fluorophosphonate (3). To decide between these reactions, half of the above hydrolysis product was rendered

$$(C_3H_7O)_2POF + 4NaOH = Na_2PO_4 + NaF + H_2O + 2C_3H_7{\cdot}OH \quad . \quad . \quad . \quad . \quad (1)$$

$$(C_3H_7O)_2POF + 2NaOH = (C_3H_7O)_2PO{\cdot}ONa + NaF + H_2O \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$(C_3H_7O)_2POF + 2NaOH = (NaO)_2POF + 2C_3H_7{\cdot}OH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

acid to bromophenol-blue with dilute nitric acid, and the sodium fluoride determined as PbClF : it corresponded to 41·1 g. (0·98 mol.) per mol. of di*iso*propyl fluorophosphonate. The hydrolysis is therefore in accordance with equation (2).

A small portion of the hydrolysis solution was strongly acidified with concentrated nitric acid, and warm ammonium molybdate solution added. No visible change took place, and it was only after some minutes' boiling that a yellow coloration was produced. This is good evidence against equation (1). Presumably sodium di*iso*propyl phosphate requires to be broken down with boiling nitric acid before phosphoric acid is produced.

Hydrolysis by N/2*-sodium hydroxide at room temperature.* (a) Di*iso*propyl fluorophosphonate (2·0532 g.) was shaken with 100 ml. of 0·49N-sodium hydroxide at 17°. The oily drops disappeared only after about 5 minutes. The shaking was continued for a total of 30 minutes, and then 25 ml. were withdrawn and required 13·35 ml. of 0·5N-sulphuric acid for neutralisation (phenolphthalein). Therefore 1 mol. of the fluorophosphonate had reacted with 1·994 mols. of alkali.

(b) Di*iso*propyl fluorophosphonate (2·3355 g.) was allowed to *stand* in contact with 100 ml. of 0·49N-sodium hydroxide without shaking. After 30 minutes a considerable amount of unchanged oil still remained, and titration showed that hydrolysis had proceeded to an extent of about 16%. This result is important in indicating that decontamination by cold dilute alkali is effective only when accompanied by vigorous agitation. This point should be borne in mind when dealing with apparatus contaminated by di*iso*propyl fluorophosphonate.

Pure Diammonium Fluorophosphonate.—When prepared according to the method of Lange and Krüger (*loc. cit.*), diammonium fluorophosphonate contains ammonium phosphate and ammonium difluorophosphonite, $(NH_4O)POF_2$. Diammonium fluorophosphonate (50 g.) was dissolved in a mixture of methyl alcohol (600 c.c.) and water (200 c.c.). The mixture was filtered, and the clear solution left overnight. The crystals (20 g.) which had separated were filtered off, washed with methyl alcohol, and dried in a vacuum desiccator. The pure compound is colourless and sublimes at *ca.* 230° [Found : NH_4, 24·0; F, 12·3. Calc. for $(NH_4)_2PO_3F,H_2O$: NH_4, 23·68; F, 12·5%].

Disilver Fluorophosphonate.—Good samples were prepared by adding the calculated quantity of silver nitrate in concentrated aqueous solution to the calculated quantity of diammonium fluorophosphonate also in concentrated aqueous solution, and leaving the mixture in an ice-chest for 2 hours. The solid which separated was washed with a small quantity of cold water, alcohol, and then ether, and dried in a desiccator screened from light.

With impure samples of diammonium fluorophosphonate containing ammonium phosphate, a yellow precipitate of silver phosphate was produced on the addition of silver nitrate solution. The silver phosphate was filtered off and the calculated quantity of powdered silver nitrate was then stirred into

* *Recent References added in Proof*—Whitby (*Practitioner*, 1947, 243); J. P. Quilliam and T. A. Quilliam (*Medical Press*, 1947, Oct. 22nd).

the solution until dissolved. The solution was then treated as above. It was sometimes necessary to add alcohol to the cold solution to promote separation of the silver fluorophosphonate.

Diisopropyl Fluorophosphonate from Silver Fluorophosphonate.—Dry silver fluorophosphonate (62·8 g., 0·2 mol.) was added to a solution of *iso*propyl iodide (76·5 g., 0·4 mol.) in dry toluene (120 c.c.). Heat was evolved and the gentle ebullition which occurred was maintained for 30 minutes. After cooling, the silver iodide was filtered off, and the filtrate distilled, the fraction, b. p. 75—89°/23 mm. (17·0 g.), being collected. This was distilled several times until a fraction, b. p. 74—75°/17 mm., was collected (Found: F, 10·1. Calc. for $C_6H_{14}O_3PF$: F, 10·32%).

Diethyl Fluorophosphonate.—Diethyl chlorophosphonate (103·6 g., 0·6 mol.), dry sodium fluoride (54·6 g., 1·3 mol.), and dry benzene were heated under reflux with vigorous stirring for 2 hours. The product was then cooled, filtered (kieselguhr), and the benzene distilled off under reduced pressure. The residue (84·5 g.; 90·3%) distilled almost entirely at 76—77°/25 mm., and had b. p. 63°/12 mm., 70—72°/18 mm., 74—76°/23 mm., 171°/760 mm. (Found: F, 12·2; Cl, nil. Calc. for $C_4H_{10}O_3PF$: F, 12·17%).

From silver fluorophosphonate. To silver fluorophosphonate (62·8 g.) suspended in benzene (800 c.c.) was added dry ethyl iodide (68·8 g., 10% excess), and the mixture heated under reflux, with stirring, for 30 minutes. After removal of silver iodide, the filtrate was distilled under reduced pressure and the fraction, b. p. 88—90°/45 mm., was collected and shown to be pure diethyl fluorophosphonate. Lange and Krüger carried out their reaction in a sealed tube and used no solvent; their yield from the silver salt was only 24%. Ether could also be used as solvent, but the reaction was slower than with benzene.

Diisopropyl Fluorophosphonate: "One-stage" Process.—*iso*Propyl alcohol (180 g., 3 mols.) was dissolved in carbon tetrachloride (100 c.c.), and phosphorus trichloride (137·5 g., 1 mol.) added slowly without external cooling. It was necessary for the mixture to warm to *ca.* 50—60° in order to allow the reaction to proceed at a reasonable speed. When the addition was complete, the mixture was kept under reduced pressure with a stream of dry air passing through it for 1 hour. The product was chlorinated at 0° by a moderate stream of chlorine, until a permanent green coloration was obtained (about 2 hours). The liquid was then treated with a stream of dry air under reduced pressure to remove excess of chlorine and hydrogen chloride. This usually took about 3 hours, although the period could often be substantially reduced. (It did seem essential, however, to remove as much hydrogen chloride as possible before fluorination.) The fluorination was carried out by adding another quantity of carbon tetrachloride (about 40 c.c.) to replace that lost by evaporation, and then adding dry sodium fluoride (94·5 g., 2·25 mols.). The mixture was mechanically stirred and then warmed. After the initial fairly vigorous reaction had subsided, the mixture was gently refluxed for 3 hours, during which time no fuming occurred. The product was cooled, filtered, and the carbon tetrachloride distilled off under reduced pressure, and the residual liquid distilled. A very small fraction was collected at 70—75°/21 mm., followed by the main fraction (138 g.; 75%, based on phosphorus trichloride) at 78—84·5°/21 mm. of very nearly pure di*iso*propyl fluorophosphonate. This main fraction distilled almost entirely at 82—83°/21 mm. giving the pure compound (Found: F, 10·25%).

Mixtures of 2 : 2′-Dichlorodiethyl Sulphide and Diisopropyl Fluorophosphonate.—The freezing points of mixtures of 2 : 2′-dichlorodiethyl sulphide (H) and di*iso*propyl fluorophosphonate (FP) were determined. Cooling agents used were ice, ice–salt, acetone–solid carbon dioxide, and liquid air. The H used had *d* 1·275 g./c.c., and the FP had *d* 1·067 g./c.c., at 19°

H (%).	FP (%).	M. p.	H (%).	FP (%).	M. p.	H (%).	FP (%).	M. p.
100	0	11·5°	61·44	38·56	0·4°	37·42	62·58	−11°
90·54	9·46	8·9	54·46	45·54	− 3·3	42·76	57·24	− 7·5
82·73	17·27	6·3	0	100	*ca.* −82	47·27	52·73	− 5·4
76·11	23·89	4·8	13·00	87·00	−36	51·11	48·89	− 4·2
68·21	31·79	2·8	22·99	77·01	−22	54·46	45·54	− 3·3
65·66	34·34	2·1	31·94	69·06	−15			

The following were exposed to various concentrations of the different fluorophosphonates (mentioned in this and subsequent papers) dispersed in a 10 m.³ chamber: F. J. Buckle, N. B. Chapman, H. G. Cook, R. Heap, J. D. Ilett, B. A. Kilby, H. McCombie, F. L. M. Pattison, B. C. Saunders, F. E. Smith, G. J. Stacey, F. Wild, I. G. E. Wilding, S. J. Woodcock.

Toxicity experiments on animals were carried out by B. A. Kilby *et al.*

We are indebted to the Chief Scientist, Ministry of Supply, for permission to publish this paper.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, May 19th,* 1947.]

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139. *Esters containing Phosphorus. Part V. Esters of Substituted Phosphonic and Phosphonous Acids.*

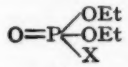
By B. C. SAUNDERS, G. J. STACEY, F. WILD, and I. G. E. WILDING.

A variety of diethyl esters of substituted phosphonic acids (I) has been prepared. Unless X = F, the compounds described are relatively non-toxic by inhalation and are devoid of miotic action. If the fluorine atom is separated from the phosphorus atom by the CH_2 group, the toxic properties of the compound are greatly diminished. *Diethyl 2-fluoroethylphosphonate* has been prepared by the Arbusow rearrangement and by an independent method.

The preparation of a new type of ester, *viz.*, *ethyl difluorophosphonite*, is described.

Bistriethyl-lead fluorophosphonate possesses powerful sternutatory properties.

In Part IV (preceding paper) it was reported that diethyl fluorophosphonate (I, X = F) was toxic by inhalation and produced powerful miosis. The present communication is concerned mainly with a discussion of phosphonic esters of type (I) in which X is varied. Diethyl hydrogen phosphite and diethyl chlorophosphonate (I; X = Cl), (Part I, McCombie, Saunders, and Stacey, *J.*, 1945, 380) were found to be non-toxic by inhalation and did not produce any miotic effect. Similar remarks apply to diethyl hydrogen phosphate (X = OH), diethyl ethylphosphonate (X = Et), and triethyl phosphate (X = OEt).


(I.)

The investigation was then extended to a wide range of new compounds. These compounds were originally described in reports on fluorophosphonates to the Ministry of Supply, Dec. 18th, 1941, onwards.

Potassium thiocyanate reacted readily with diethyl chlorophosphonate giving *diethyl thiocyanatophosphonate*:

$$Et_2PO_2Cl + KSCN = Et_2PO_2SCN + KCl$$

Diethyl cyanophosphonate (II) was not obtained in any appreciable yield by the action of potassium cyanide on the chlorophosphonate, but was prepared by the novel reaction (*A*):

$$P(OEt)_3 + CNI = O{:}P(CN)(OEt)_2 + EtI \quad . \quad . \quad . \quad . \quad . \quad . \quad (A)$$
(II.)

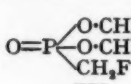
Both the thiocyanatophosphonate and the cyanophosphonate were relatively non-toxic. For example, a concentration of 1 mg./l. of (II) killed 1 out of a batch of 23 small animals. The L.D. 50 for intravenous injection into rabbits was about 4 mg./kg. The symptoms appeared to be purely asphyxial (typical of cyanide rather than of fluorophosphonate). The L.D. 50 for subcutaneous injection into mice was 25 mg./kg.

Gaseous ammonia reacted with the chlorophosphonate at 0° producing solid diethyl aminophosphonate in accordance with the equation:

$$Et_2PO_2Cl + 2NH_3 = Et_2PO_2NH_2 + NH_4Cl$$

In a similar manner gaseous methylamine gave diethyl methylaminophosphonate, Et_2PO_2NHMe, which was, however, a liquid. The compound could not be acetylated with a mixture of acetic acid and acetic anhydride, and it did not react with either *p*-toluenesulphonyl chloride or ethylene oxide. Diethyl anilinophosphonate has previously been described (Part I, *loc. cit.*). *Diethyl morpholinophosphonate* has now been prepared by a similar method. The aminophosphonate, the methylaminophosphonate, and the anilinophosphonate were non-toxic and devoid of miotic properties.

It was important to determine whether the fluorine atom must be attached directly to the phosphorus atom in order to produce "fluorophosphonate-like" activity. For this purpose we treated the highly toxic di-*sec.*-butyl fluorophosphonate (to be described later in this series) with diazomethane and obtained a compound which was undoubtedly *di*-sec.-*butyl fluoromethylphosphonate* (III). Unlike the parent fluorophosphonate, the fluoromethylphosphonate was only slightly toxic and produced negligible miosis. It may be mentioned here that thionyl chloride and carbonyl chloride were converted by means of diazomethane into *bis*(*chloromethyl*) *sulphoxide* and *s*-dichloroacetone respectively.


(III).

The next stage was to prepare a compound with a second methylene group between the fluorine and the phosphorus atom. *Diethyl 2-fluoroethylphosphonate* (IV) was prepared by the action of bromofluoroethane on sodium diethyl phosphite. This reaction was first recorded in "Summary of Work carried out for the Ministry of Supply during the period Jan. 1st—March 1st, 1945" and was the first recorded example of the 2-fluoroethyl group attached to phosphorus. Compound (IV) is of special interest in that it showed neither the toxic properties of the fluorophosphonates nor to any appreciable extent the toxic action associated with the "fluoroacetates". This may mean that the animal body is probably unable to break the P–C link easily, as shown in equation (*B*), otherwise the compound would have produced the convulsions typical of fluoroethyl alcohol when inhaled by animals (cf. McCombie and Saunders, *Nature*, 1946, **158**, 382).

$$(EtO)_2PO{\cdot}CH_2{\cdot}CH_2F + H_2O = (EtO)_2P{\cdot}OH + HO{\cdot}CH_2{\cdot}CH_2F \quad . \quad . \quad . \quad (B)$$
(IV.)

Diethyl benzylphosphonate was prepared in a similar manner using benzyl chloride in place of bromofluoroethane. When *p*-toluenesulphonyl chloride and naphthalene-2-sulphonyl chloride

were allowed to react with sodium diethyl phosphite, the corresponding disulphones were obtained in small yield.

Arbusow (*Chem. Zent.*, 1906, II, 1640) demonstrated the ready " isomerisation " of trimethyl phosphite to dimethyl methylphosphonate by heating it with methyl iodide.

This method was then extended, and diethyl 2-fluoroethylphosphonate (IV) and diethyl benzylphosphonate were readily prepared by heating triethyl phosphite with bromofluoroethane and benzyl chloride respectively:

$$P(OEt)_3 + Br\cdot CH_2\cdot CH_2F = O{:}P(OEt)_2\cdot CH_2\cdot CH_2F + C_2H_5Br \quad . \quad . \quad . \quad (C)$$

Reaction (*C*) depended upon the difference in reactivity between the bromine and the fluorine atom in bromofluoroethane. Nevertheless some tetraethyl ethylene-1:2-diphosphonate, $(EtO)_2PO\cdot CH_2\cdot CH_2\cdot OP(OEt)_2$, was also produced in this reaction (*C*) and in reaction (*A*). The diphosphonate was non-toxic.

The 2-chloroethyl group, which is often an effective toxophore, was then attached to phosphorus through oxygen. No reaction appeared to take place between ethylene chlorohydrin and diethyl chlorophosphonate in the absence of a tertiary base. In the presence of pyridine, however, which removed the hydrogen chloride formed, a smooth reaction took place at 0° with the formation of *diethyl 2-chloroethyl phosphate*, $O{:}P(OEt)_2\cdot O\cdot CH_2\cdot CH_2Cl$ (V.), in good yield. The compound was non-toxic and devoid of miotic action. The fluorine analogue of (V), *diethyl 2-fluoroethyl phosphate*, was prepared in an analogous manner from 2-fluoroethyl alcohol. It proved to be non-toxic by injection.

Ethyl difluorophosphonite (VI) was obtained by the action of sodium fluoride on the corresponding dichlorophosphonite; unlike diethyl fluorophosphonate, it was rapidly attacked by cold water. Alcohol converted (VI) into the fluorophosphonate:

$$O{:}PF_2\cdot OEt + EtOH = O{:}PF(OEt)_2 + HF$$
(VI.)

When mice, rats, rabbits, and guinea-pigs were exposed to a concentration of 0·88 mg./l. (*i.e.*, 1 in 5,000) of ethyl difluorophosphonite for 10 minutes there was irritation of the eyes and nose with nasal discharge, lachrymation, and salivation. Four minutes after exposure the mice and some of the rats developed dyspnœa, but all the animals recovered. When animals were exposed to a corresponding concentration of ethyl dichlorophosphonite (1·46 mg./l.; 1 in 5,000) similar symptoms were observed and no deaths resulted.

It has been shown (McCombie and Saunders, *Nature*, 1947, **159**, 491) that triethyl-lead salts are, in general, sternutators. Accordingly *bistriethyl-lead fluorophosphonate*, $O{:}PF(O\cdot PbEt_3)_2$, was prepared in an attempt to combine sternutatory properties and miotic action. A solid with powerful sternutatory properties, it produced an irrespirable atmosphere at a concentration of 1 part in 10^6. At 1 part in 10^8 the sternutatory properties were still marked. No miotic effect was produced in human beings at a concentration of 1 part in 10^6. Tests at higher concentrations were not carried out on human beings owing to the overwhelming sternutatory effects.

Experimental.

Diethyl Thiocyanatophosphonate.—Diethyl chlorophosphonate (34·5 g., 0·2 mol.) was gently warmed under reflux with dry, finely-powdered, potassium thiocyanate (24·3 g., 0·25 mol.). A reaction soon began and a finely-divided white precipitate gradually separated. Heat was applied to maintain very gentle ebullition for 15 minutes. After cooling, the solid was filtered off and thoroughly drained, and the filtrate was distilled under reduced pressure. Two fractions were collected: (i) b. p. 40°/13 mm.; (ii) b. p. 112—116°/13 mm. Fraction (i) was redistilled and gave 5·3 g. of the *thiocyanatophosphonate* (Found: S, 16·9; P, 15·6. $C_5H_{10}O_3NSP$ requires S, 16·4; P, 15·9%).

Diethyl Cyanophosphonate.—Triethyl phosphite (41·5 g., 0·25 mol.) was dissolved in dry ether (500 c.c.) and to this solution iodine cyanide (38·75 g., 0·25 mol.) dissolved in dry ether (100 c.c.) was slowly added. At first there was a vigorous reaction, but no free iodine was produced until the addition was complete; a brown coloration then slowly developed. Ether and other volatile fractions were removed on the water pump at ordinary temperatures during 1½ hours. Almost the entire residue then distilled at 93—98°/14 mm. This was redistilled, and the *cyanophosphonate*, b. p. 95—97°/14 mm., collected. Yield, 18·7 g. (46%). B. p. 90—91°/11 mm. (Found: CN, 15·3. $C_5H_{10}O_3NP$ requires CN, 15·9%).

Diethyl Aminophosphonate.—Diethyl chlorophosphonate (20 g.) was dissolved in dry ether (250 c.c.), cooled in ice, and a stream of dry ammonia passed into the solution until no more solid was precipitated. After removal of ammonium chloride (6·2 g., 100%), the ether was distilled and the residue solidified on standing. Recrystallisation was difficult, and therefore the solid was purified by distillation at 131—138°/0·2 mm.; the white crystalline product (m. p. 54·5°, yield, 14 g.) contained N and P, and was Cl-free (Found: C, 31·6; H, 8·46. Calc. for $C_4H_{13}O_3NP$: C, 31·4; H, 7·9%). This compound was first described in Report to the Ministry of Supply Aug. 8th, 1942. Later Atherton, Openshaw, and

Todd (*J.*, 1945, 662) prepared it by a different method. Their description of the compound agrees with ours, and differs from that given by Pitschimuka (*J. pr. Chem.*, 1911, **84**, 753).

Diethyl Methylaminophosphonate.—Diethyl chlorophosphonate (20 g.) was dissolved in dry ether (200 c.c.), and dry methylamine was passed into the solution which was cooled in ice–water. A white precipitate was produced and heat evolved. When no more solid separated, the stream of methylamine was stopped and the mixture filtered. The ether was distilled from the filtrate and the residue fractionated under reduced pressure. The fraction (16·3 g., 84%), b. p. 130°/15 mm., contained P and was Cl-free (Found : N, 8·7. Calc. for $C_5H_{14}O_3NP$: N, 8·4%). We had previously prepared this compound from the unstable iodophosphonate (Part III, *J.*, 1945, 921).

Diethyl Morpholinophosphonate.—To a solution of diethyl chlorophosphonate (4·3 g., 0·025 mol.) in ether (25 c.c.), cooled in ice–water, morpholine (4·4 g., 0·05 mol.) was added drop by drop. When the addition was complete, more ether (15 c.c.) was added and the whole gently warmed under reflux. The solid which had separated was filtered off, ether removed from the filtrate, and the residue distilled. The *morpholinophosphonate* had b. p. 137°/11 mm. Yield, 4·4 g. (79%) (Found : C, 43·55; H, 8·19; N, 6·22. $C_8H_{18}O_4NP$ requires C, 43·04; H, 8·13; N, 6·28%).

Reaction between Diazomethane and Carbonyl Chloride.—Diazomethane was prepared from nitrosomethylurea (20·6 g.), ether (200 c.c.), and sodium hydroxide (60 c.c. of 50% aqueous solution) (*Org. Synth.*, X), and dissolved in ether at 0°. The ethereal solution was dried (KOH) for 10 minutes and poured from the drying-agent. A slow stream of carbonyl chloride was passed into the cooled solution for 1 hour, the temperature being kept below 5°. After removal of the ether, the residue distilled at 173°. The liquid (3·5 g.) solidified to a white crystalline mass, m. p. and mixed m. p. with authentic dichloroacetone, 44° (Found : C, 28·6; H, 3·18. Calc. for $C_3H_4OCl_2$: C, 28·3; H, 3·15%).

Reaction between Diazomethane and Thionyl Chloride.—Diazomethane (from 41·0 g. of nitrosomethylurea) in ether, dried as above, was cooled to 0° and thionyl chloride (10 g.) was added slowly, the temperature being kept below 5°. After removal of the ether, the residue was distilled and two fractions were collected : (i) b. p. 45°/0·7 mm., (3 g.); (ii) b. p. 55°/0·7 mm., (5 g.). Fraction (ii) gave a solid, m. p. 39° (Found : C, 16·4; H, 2·77. $C_2H_4OCl_2S$ requires C, 16·3; H, 2·74%).

Di-sec.-*butyl Fluoromethylphosphonate.*—Diazomethane (25% excess) in ethereal solution was added slowly to di-*sec.*-butyl fluorophosphonate (10 g.) dissolved in dry ether (50 c.c.) cooled in ice. The colour of the diazomethane was gradually discharged, and the reaction was at no time vigorous. The mixture was left in ice for 3 hours, and then the ether was distilled off. On distillation of the residue, a fraction (5 g.), b. p. 96—100°/3 mm., was obtained (Found : F, 13·46, 13·5. $C_9H_{20}O_3FP$ requires F, 13·7%).

Diethyl 2-*Fluoroethylphosphonate.*—Sodium diethyl phosphite was prepared from sodium methoxide (32·4 g., 0·6 mol.) and diethyl hydrogen phosphite (32·8 g., 0·6 mol.) in dry ether (700 c.c.). Bromofluoroethane (80·0 g., 0·64 mol.) was then added and the whole heated under reflux for 6 hours, during which time a white solid separated. After 8 hours the solid (mainly sodium bromide) was filtered off. The ether was distilled from the filtrate and the mixture distilled under reduced pressure. A fraction (30 g.), b. p. 70—80°/20—11 mm., was collected; the temperature then rose, and a fraction, b. p. 198—201°/11 mm., came over. The lower fraction was redistilled at 74—75°/11 mm. and proved to be the *fluoroethylphosphonate* identical with the compound obtained by the Arbusow rearrangement (below). The higher fraction deposited a very small amount of solid on standing, and was purified by passing it through ½ in. of animal charcoal on a No. 3 sintered plate, and redistilling at 200—202°/14 mm. The product, a colourless liquid, contained P and was halogen-free. It was undoubtedly *tetraethyl ethylene*-1 : 2-*diphosphonate* (Found : C, 37·1; H, 7·83. $C_{10}H_{24}O_6P_2$ requires C, 39·7; H, 7·95%).

Sodium Diethyl Phosphite.—The sodium diethyl phosphite required in subsequent preparations was prepared as follows. Sodium dust (46 g., 2·0 at.) in dry ether (600 c.c.) was placed in a flask fitted with a reflux condenser, and diethyl hydrogen phosphite (276 g., 2·0 mol.) was added from a dropping-funnel. It was necessary to exercise care during the early stages of the addition because the reaction (an exothermic one) was usually delayed. (If a large quantity of the hydrogen phosphite was added before the reaction started, the mixture would subsequently boil violently with frothing, and the finely-powdered sodium would ignite on exposure to the air.)

During the reaction between sodium diethyl phosphite and an organic halide, the sodium halide often separated in a colloidal condition. It could be coagulated by the addition of about 6 times the original volume of ether, but as this procedure was rather wasteful, the solid was usually filtered off as completely as possible, washed with a small quantity of ether, and the filtrate distilled; it still contained traces of colloidal sodium halide.

Diethyl Benzylphosphonate.—To sodium diethyl phosphite, prepared from diethyl hydrogen phosphite (27·6 g., 0·2 mol.) and sodium (4·6 g., 0·2 at.) in dry ether (200 c.c.), benzyl chloride (25·2 g., 0·2 mol.) was added, and the whole heated under reflux for 4 hours and then worked up as above. After removal of the ether, the residue was fractionated and the *benzylphosphonate*, b. p. 155°/14 mm., collected. Yield, 21 g. (45%) (Found : C, 55·7; H, 7·36; P, 13·55. $C_{11}H_{17}O_3P$ requires C, 57·8; H, 7·46; P, 13·6%).

Reaction between Sodium Diethyl Phosphite and p-*Toluenesulphonyl Chloride.*—To sodium diethyl phosphite (0·5 mol.) in dry ether (800 c.c.), *p*-toluenesulphonyl chloride (100 g., 1·02 mol.) was added slowly. The reaction, which was vigorous at first, moderated later. After heating under reflux for one hour, the solid (*S*) formed was filtered off.

After removal of the ether from the filtrate, *p*-toluenesulphonyl chloride (70 g.) separated and was recrystallised from light petroleum; m. p. and mixed m. p. 66—68°.

The solid (*S*) was washed with hot water (100 c.c.) to remove inorganic salts, and the residue was recrystallised from 90% acetic acid giving colourless needles, m. p. 204°. Yield, 1·8 g. (Found : C, 54·06; H, 4·55; S, 20·8. Calc. for $C_{14}H_{14}O_4S_2$: C, 54·2; H, 4·52; S, 20·64%).

Naphthalene-2-sulphonyl chloride behaved in a similar manner. The disulphone was recrystallised from aqueous acetic acid and then twice from benzene; m. p. 188° (Found : C, 62·5; H, 3·91; S, 16·4. Calc. for $C_{20}H_{14}O_4S_2$: C, 62·8; H, 3·67; S, 16·75%).

Diethyl Ethylphosphonate.—A mixture of triethyl phosphite (33·2 g., 0·2 mol.) and ethyl iodide

(31·2 g., 0·2 mol.) was heated under reflux for 12 hours. After removal of ethyl iodide, the entire product distilled at 90—92°/16 mm. Yield, 31·2 g. (94%).

Diethyl 2-Fluoroethylphosphonate.—Triethyl phosphite (24·9 g.) and bromofluoroethane (18·9 g.) were gently heated under reflux for 1 hour. The product was distilled, and fractions, b. p. 86·5—88°/18 mm. and 203—206°/15 mm., were collected. The first fraction was redistilled at 74—75°/11 mm. The liquid (7·4 g., 17%) contained P (Found: F, 10·8. $C_6H_{14}O_3FP$ requires F, 10·3%). The higher fraction was the diphosphonate.

Diethyl Benzylphosphonate.—Triethyl phosphite (24·9 g.) and benzyl chloride (17·1 g.) were heated under reflux in an oil-bath at 150—160° for 10 hours. The gas evolved was condensed in an ice–hydrochloric acid trap, and identified as ethyl chloride by conversion into tetraethylammonium chloride. The benzylphosphonate (14·8 g., 74%) was collected at 169—171°/25 mm.

Diethyl 2-Chloroethyl Phosphate.—Diethyl chlorophosphonate (86·3 g., 0·5 mol.) was added slowly to a mixture of ethylene chlorohydrin (40·3 g., 0·5 mol.) and pyridine (39·6 g., 0·5 mol.) cooled in ice–water. After the addition, the mixture was left for 1 hour and then the solid which had separated was filtered off and washed with ether. After removal of the ether, the fraction, b. p. 139—148°/17 mm., was collected. On redistillation, the *chloroethyl phosphate* had b. p. 144—145°/18 mm. Yield, 76·7 g. (Found: Cl, 16·20; 16·44. $C_6H_{14}O_4ClP$ requires Cl, 16·3%). (In the determination by the Carius method it was necessary to use at least 3 c.c. of fuming nitric acid per 0·4 g. of ester to prevent the formation of viscous material.)

Diethyl 2-Fluoroethyl Phosphate.—Diethyl chlorophosphonate (43 g.) dissolved in dry ether (25 c.c.) was added slowly to a mixture of fluoroethyl alcohol (16 g.) and dry pyridine (20 c.c.) in dry ether (25 c.c.) cooled in ice–water. After the addition, the mixture was left for 30 minutes and then the pyridine hydrochloride was filtered off. The filtrate was dried (Na_2SO_4), the ether removed, and the residue fractionated and collected at b. p. 123—124°/13 mm. Yield, 30 g. (Found: C, 36·3; H, 6·6; F, 9·5. $C_6H_{14}O_4FP$ requires C, 36·0; H, 7·0; F, 9·5%).

Ethyl Dichlorophosphonite.—Ethyl alcohol (54 g.) was added slowly to phosphorus oxychloride (180 g.) in dry ether (210 c.c.) cooled to 5°. After 2 hours, the product was distilled under reduced pressure; ether, hydrogen chloride, and unchanged alcohol were first removed, and the fraction of b. p. 63°/19 mm. was collected. Yield, 157 g. (83%) (Found: Cl, 44·1. Calc. for $C_2H_5O_2Cl_2P$: Cl, 43·5%).

Ethyl Difluorophosphonite.—Ethyl dichlorophosphonite (53·5 g.) and sodium fluoride (29·3 g.; 10% excess) were mixed in a flask cooled in ice–water. The flask was fitted with a water condenser to the end of which were attached (*a*) a conical flask to act as a trap, (*b*) a liquid-air trap, arranged in series. After about 1 minute a vigorous reaction set in and the gaseous products condensed in the traps. The reaction was completed by warming the mixture for 10 minutes. The crude material (20 g.) in the traps was fractionated, and 12·2 g. of the *difluorophosphonite*, b. p. 85—86°, were collected. The product contained P, was Cl-free, and reacted readily with cold water (Found: F, 29·47. $C_2H_5O_2F_2P$ requires F, 29·23%).

Reaction between Ethyl Alcohol and Ethyl Difluorophosphonite.—Ethyl alcohol (4·6 g.) was added to freshly prepared ethyl difluorophosphonite (6·5 g.), and the mixture left for 2 hours. The reaction was completed by heating on a water-bath for 30 minutes. The product was then distilled under reduced pressure; the distillate on refractionation gave diethyl fluorophosphonate (1·6 g.), b. p. 168—171°.

Bistriethyl-lead Fluorophosphonate.—Silver fluorophosphonate (9·5 g.) suspended in dry benzene (50 c.c.) was added to triethyl-lead chloride (20 g.) also in dry benzene (50 c.c.), and the mixture refluxed for 3 hours, cooled, and filtered. The solid was extracted with boiling ethyl acetate from which a colourless solid (m. p. indef. >260°) separated. Yield, 11 g. The *compound* contained F and P and was soluble in acetone (Found: Pb, 60·59. $C_{12}H_{30}O_3FPPb_2$ requires Pb, 60·36%).

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140. *Strychnine and Brucine. Part XLIX. A New Method for the Preparation of Pseudostrychnine.*

By A. S. BAILEY and SIR ROBERT ROBINSON.

It is found that strychnine *N*-oxide is changed into pseudostrychnine (hydroxystrychnine) by treatment with an aqueous solution of potassium chromate at 100°. This process is the best available for the preparation of the substance. In the brucine series the yield is less favourable, and one of Leuchs's brucones is obtained as a by-product.

FREUND and SPEYER (*Ber.*, 1911, **44**, 2339) found that treatment of the *N*-oxide of codeinesulphonic acid with potassium chromate gave formaldehyde and a substance believed to be $C_{18}H_{23}O_8NS$ but which on de-sulphonation afforded $C_{17}H_{19}O_3N$, isomeric with morphine. Diels and Fischer (*Ber.*, 1916, **49**, 1721) showed that this base is norcodeine previously obtained by the ethyl azodicarboxylate method (*idem, Ber.*, 1914, **47**, 2043), also that the Freund and Speyer product is $C_{17}H_{19}O_6NS$ and further that this *N*-demethylation procedure can be applied to codeine itself. Although advantage has been taken of these observations in the manufacture of *N*-allylnorcodeine, very few, if any, further applications of the method have been reported.

It occurred to us that it might well be generally available for the fission of tertiary amines, and that in a polycyclic system the result should be the formation of a carbinol-amine. Thus in the case of strychnine the product should be pseudostrychnine or an isomeride.

Actually, pseudostrychnine is obtained as the modification of higher melting point, convertible into that of lower melting point by the known methods. The formation of this modification is doubtless connected with the fact that it crystallises from a hot aqueous solution, and the plausible analogy with the separation of β-glucose under similar conditions is under examination.

The smooth reaction here realised leads us to suggest that the oxidation of strychnine by atmospheric oxygen in the presence of co-ordinated cupric derivatives (Leuchs, *Ber.*, 1937, **70**, 1543) takes a similar course. Indeed, strychnine *N*-oxide was actually isolated a by-product of the oxidation.

This view is supported by the fact that the action of potassium chromate on brucine *N*-oxide affords pseudobrucine together with that brucone which Leuchs and Boit (*Ber.*, 1940, **73**, 884) obtained as one of the products of the catalysed aerial oxidation of brucine. The potassium chromate may be replaced, but without advantage, by an equivalent amount of chromic acid or potassium dichromate.

Experimental.

Pseudostrychnine.—As usually prepared, strychnine *N*-oxide contains hydrogen peroxide which replaces a part of the water in the crystals. This affects the yield adversely and the following method was adopted.

A mixture of strychnine (50 g.), water (150 c.c.), and hydrogen peroxide (30 c.c. of 30%) was heated for 1 hour at 100°, boiled for 5 minutes, filtered, and cooled. The separated crystals were dissolved in hot water (120 c.c.) and the solution boiled for 5 minutes with platinum wire; 53 g. (88%) of the hydrated *N*-oxide separated; m. p. 205—207° (Pictet, *Ber.*, 1907, **40**, 1172, gives m. p. 207°).

A solution of this material (20 g.) in water (100 c.c.) was heated in boiling water, and potassium chromate (1 g.) in water (5 c.c.) added. After 5—10 minutes the solution clouded and soon filled with long needles; the reaction was completed in 45 minutes. The mixture was cooled, the solid collected, washed with water, and ether, and dried in a vacuum over phosphoric anhydride (yield, 15—17 g.) (Found: loss at 100° in a vacuum, 7·7. $C_{21}H_{22}O_3N_2,1{\cdot}5H_2O$ requires 7·2%). The water is lost at 180—190°, and the substance then had m. p. 253—257 (decomp.) with previous sintering (Leuchs, *loc. cit.*, gives m. p. 262°, and Warnat, *Helv. Chim. Acta*, 1931, **14**, 999, gives m. p. 268°). This product is sufficiently pure for many purposes. It was crystallised by addition of ether to its solution in chloroform, and was then dissolved in dilute hydrochloric acid and precipitated with ammonia. This treatment afforded the lower melting isomeride, m. p. 235—237° (decomp.), $[\alpha]_D^{18°}$ − 63° (*c*, 1·63 in chloroform) (Leuchs, *loc. cit.*, gives m. p. 233°, $[\alpha]_D^{20°}$ − 69°) (Found in material dried in high vacuum at 130°: C, 71·7; H, 6·5; N, 8·3. Calc. for $C_{21}H_{22}O_3N_2$: C, 72·0; H, 6·3; N, 8·0%).

The perchlorate crystallised from water in stout needles which in agreement with Blount and Robinson (*J.*, 1932, 2305) darkened at 235—240° but did not melt at 300° (Leuchs, *Ber.*, 1937, **70**, 1703, reports that the salt sinters at 250° and decomposes at 260—270°) (Found: loss at 100° in a vacuum, 0·9%; in dried material, C, 55·5; H, 5·2; N, 6·2; Cl, 7·8. Calc. for $C_{21}H_{22}O_3N_2,HClO_4$: C, 55·9; H, 5·1; N, 6·2; Cl, 7·9%).

The methyl ether was prepared from the crude reaction product in the usual manner; it crystallised from methanol in long needles, m. p. 196—198° (decomp.), $[\alpha]_D^{15°}$ − 64° (*c*, 0·89 in chloroform) (Found: C, 72·0; H, 6·7. Calc. for $C_{22}H_{24}O_3N_2$: C, 72·5; H, 6·6%). Warnat (*loc. cit.*) gives m. p. 198—200°, $[\alpha]_D^{20°}$ − 70°; Leuchs (*loc. cit.*) gives m. p. 190°, $[\alpha]_D^{20°}$ − 75°; David (private communication, material prepared according to Leuchs) finds $[\alpha]_D^{20°}$ − 69°.

The ethyl ether crystallised from ethanol in slender matted needles, m. p. 217—219° (decomp.), $[\alpha]_D^{16°}$ − 51° (*c*, 0·92 in chloroform) (Found: C, 72·9; H, 6·9; N, 7·2. Calc. for $C_{23}H_{26}O_3N_2$: C, 73·0; H, 6·9; N, 7·4%). Its benzylidene derivative, fine yellow needles from ethanol, had m. p. 205—207° (decomp.) (Found: C, 76·9; H, 6·7; N, 5·6. Calc. for $C_{30}H_{30}O_3N_2$: C, 71·3; H, 6·7; N, 6·0%). For the ethyl ether Warnat (*loc. cit.*) cites m. p. 222—224°, $[\alpha]_D^{28°}$ − 57° (David finds $[\alpha]_D^{20°}$ − 53°), and Leuchs (*loc. cit.*) states that the benzylidene derivative has m. p. 202°, and m. p. 208—209° in an evacuated capillary. The *N*-nitroso-derivative crystallised from 80% alcohol as small prisms, m. p. 288—290° (decomp.) (Found: C, 66·3; H, 5·5; N, 10·7. Calc. for $C_{21}H_{21}O_4N_3$: C, 66·4; H, 5·6; N, 11·1%). Warnat (*loc. cit.*) reports m. p. 292—294°. The reduction of pseudostrychnine to strychnine (Blount and Robinson, *J.*, 1932, 2305, cf. Leuchs, *Ber.*, 1937, **70**, 1703) was confirmed with material made by the new process. The crude product (0·8 g. from 1 g.) was washed with ether and dried, m. p. 266—270°; after crystallisation from *n*-propanol it had m. p. 275—278°; a mixture with strychnine, m. p. 277—279°, had m. p. 276—278°.

Action of Potassium Chromate on Brucine N-Oxide.—Recrystallised brucine *N*-oxide (40 g.) (prepared from 50 g. of brucine, 100 c.c. of water, and 20 c.c. of 30% hydrogen peroxide) was dissolved in water (150 c.c.), potassium chromate (4 g.) in water (10 c.c.) was added, and the solution heated in a boiling water-bath. After 3 hours the solution had become dark red, and crystals began to separate slowly after 4—5 hours, a period not shortened by seeding. The liquid was heated for 10 hours, kept overnight, and the pale yellow solid then collected and washed with water (yield, *ca.* 9 g.). This material was partly soluble in dilute mineral acid, and was separated into neutral and basic components by boiling with N-hydrochloric acid (50 c.c.) and filtering hot (solution *A*, below); the solid was washed with ether and dried, yielding 3·0 g. of a pale cream-coloured powder, m. p. 305—308° (decomp.).

The product was insoluble in dilute acid or alkali, methanol, ethanol, ethyl acetate, or acetone, moderately soluble in chloroform. It gave the brucine reaction with 5N-nitric acid, and was

best purified by dissolution in boiling acetic acid and addition of an equal volume of boiling water to the filtered solution; the substance then crystallised in small, well-formed prisms which darkened at 305° and melted to a clear brown liquid at 313—317° (the m. p. is very sensitive to the rate of heating; on rapid heating the substance had m. p. 322—325°), $[\alpha]_D^{15°}$ − 20° (*c*, 1·4 in chloroform) (Found: C, 67·2; H, 5·8; N, 6·6. Calc. for $C_{23}H_{24}O_5N_2$: C, 67·6; H, 5·9; H, 6·9%). Leuchs and Boit (*loc. cit.*) report m. p. 300—310° in a closed tube, and $[\alpha]_D^{20°}$ − 15° for the brucone isolated from the mother liquors of the catalysed aerial oxidation of brucine.

An attempted preparation of benzylidenebrucone in ethanolic sodium ethoxide afforded a yellow solid readily soluble in methanol and aqueous ethanol, but it could not be crystallised.

On addition of ammonia to the acid solution (*A*), 5·6 g. of a brown solid, m. p. 230—240° (decomp.), were precipitated. It was purified by crystallisation from chloroform–ether, followed by dissolution in dilute sulphuric acid and precipitation with ammonia, giving a solid which darkened at 240°, m. p. 255—258° (decomp.), $[\alpha]_D^{20°}$ − 64° (*c*, 1·04 in chloroform) (Found: in material dried at 120° in a vacuum: C, 67·5; H, 6·4; N, 6·3. Calc. for $C_{23}H_{24}O_5N_2$: C, 67·3; H, 6·3; N, 6·8%). Leuchs and Tessmar (*Ber.*, 1937, **70**, 2359) give m. p. 258—268° and $[\alpha]_D^{20°}$ − 65·6° for pseudobrucine.

N-Nitrosopseudobrucine was prepared like the corresponding strychnine derivative; it crystallised from ethanol–*n*-propanol in fine needles, m. p. 245—247° (decomp.) (Found: C, 62·4; H, 5·7; N, 9·8. Calc. for $C_{23}H_{25}O_6N_3$: C, 62·8; H, 5·7; N, 9·6%). Leuchs (*loc. cit.*) gives m. p. 248°.

Pseudobrucine was reduced with zinc and hydrochloric acid as described for pseudostrychnine, yielding brucine, m. p. and mixed m. p. 175—177°.

The mother liquors from several preparations were concentrated to one-third of their volume and thoroughly extracted with chloroform (6 × 50 c.c.). The dried (Na_2SO_4) solution was evaporated to a small bulk and ether added; the gum which separated soon solidified. The product contained chloroform, and was readily soluble in warm water, but only crystallised very slowly on long standing, the crystals melting at 68—73° to a cloudy liquid which lost water at 100—105° but did not appear to resolidify. Leuchs and Boit (*Ber.*, 1940, **73**, 884) state that a 1 : 1 molar mixture of brucine and brucine *N*-oxide has m. p. 72°. Reduction of the solid with sulphurous acid gave brucine, m. p. and mixed m. p. 175—178°.

Action of Potassium Chromate on Brucine N-Oxide in Presence of Hydrogen Peroxide.—Brucine (20 g.), water (60 c.c.), and 30% hydrogen peroxide (10 c.c.) were heated on a water-bath for an hour, and potassium chromate (2 g.) in water (5 c.c.) was cautiously added to the clear solution. Oxygen was evolved and the solution became deep red. After 45—60 minutes an oil separated which soon solidified. The solution was heated for 3 hours after the addition of the chromate, left overnight, the dark solid collected, and washed well with water and ether.

The product was separated into neutral and basic fractions, yielding the brucone of m. p. 315—320° (decomp.) (2·2—3·5 g.) (Found: C, 67·1; H, 5·9; N, 6·9. Calc. for $C_{23}H_{24}O_5N_2$: C, 67·6; H, 5·9; N, 6·9%).

The basic fraction was contaminated with more dark coloured material than in the previous preparation. After crystallisation from chloroform–ether followed by precipitation from sulphuric acid solution with ammonia, 4—5 g. of pseudobrucine were obtained, m. p. 255—257° (decomp.) (Found in material dried at 120° in a vacuum: C, 67·7; H, 6·5. Calc. for $C_{23}H_{24}O_5N_2$: C, 67·3; H, 6·3%).

Oxidation of Pseudobrucine to the More Fusible Brucone.—Following the directions of Leuchs, Tuschen, and Mengelberg (*Ber.*, 1944, **77**, 403), pseudobrucine (1·0 g.) was dissolved in a mixture of hydrogen peroxide (20 c.c. of 3%) and acetic acid (1 c.c.), and the mixture heated at 80° for 15 minutes. The solid which separated (0·4 g.) was collected and crystallised from methanol or water, yielding flat plates, m. p. 180—186°, $[\alpha]_D^{20°}$ − 410° (*c*, 1·4 in chloroform) (Found in material dried at 100° in high vacuum: C, 67·2; H, 6·1; N, 6·8. Calc. for $C_{23}H_{24}O_5N_2$: C, 67·7; H, 5·9; N, 6·9%). Leuchs (*loc. cit.*) gives m. p. 180—187°, $[\alpha]_D^{20°}$ − 393°. It was found that the substance, crystallised from methanol, retained solvent of crystallisation tenaciously.

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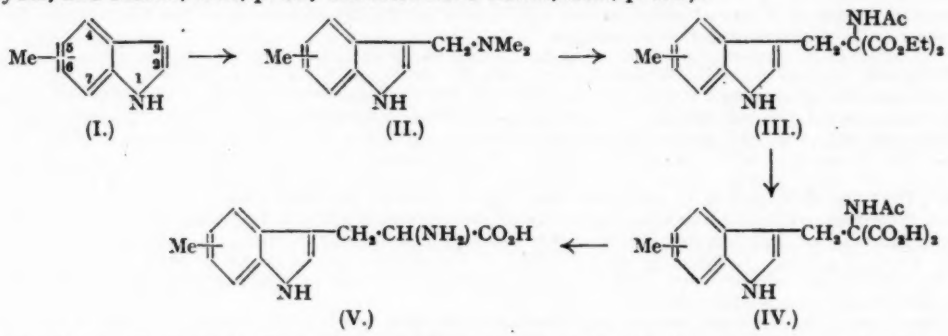
141. *The Synthesis of the Nuclear-C-methylated Tryptophans. A Note on the Aldehyde Reactions for Tryptophan.*

By H. N. RYDON.

The five possible nuclear-*C*-methylated tryptophans have been prepared from the corresponding methylindoles by the gramine synthesis of Snyder and Smith (*J. Amer. Chem. Soc.*, 1944, **66**, 350). The colours developed by these substances in the best-known "aldehyde" reactions for tryptophan are described, and some conclusions are reached regarding the mechanism of these colour reactions.

THE observation of Anderson (*Science*, 1945, **101**, 565) that 5-methyltryptophan inhibited the growth of *Bacterium coli* suggested that it would be of interest to study further the inhibitory action on bacteria of this and the other isomeric methyltryptophans, and of the related methylindoles. The preparation of these substances is recorded in the present paper; details of the biological tests, and the light the results throw on the combination of indole and tryptophan with bacterial enzymes, have been reported elsewhere (Fildes and Rydon, *Brit. J. Exp. Path.*, 1947, **28**, 211); some of these substances have proved remarkably active, *in vitro*, as inhibitors of *Salmonella typhi*.

The method used was the elegant " gramine " synthesis first worked out for tryptophan by Snyder and Smith (*loc. cit.*; cf. Albertson, Archer, and Suter, *ibid.*, p. 500) and subsequently developed by the two groups (Albertson, Archer, and Suter, *ibid.*, 1945, **67**, 36; Howe, Zambito, Snyder, and Tishler, *ibid.*, p. 38; Albertson and Tullar, *ibid.*, p. 502):



Of the five methylindoles (I) required as starting materials only two had not previously been synthesised; these, *viz.*, 4-methylindole, which had been isolated from coal-tar by Kruber (*Ber.*, 1929, **62**, 2877), and 6-*methylindole*, were prepared by cyclisation of the corresponding formylxylidines (cf. Tyson, *J. Amer. Chem. Soc.*, 1941, **63**, 2024; *Org. Synth.*, 1943, **23**, 45). Since the present work was completed, Marion and Oldfield (*Canadian J. Res.*, 1947, *B*, **25**, 1) have described similar syntheses but report no analytical data.

All the *C*-methylindoles condensed readily with formaldehyde and dimethylamine to yield the corresponding *methyl*-3-*dimethylaminomethylindoles* (" methylgramines ") (II) and these in turn condensed with acetamidomalonic ester to give the *ethyl* 1-*acetamido*-2-(x-*methyl*-3-*indolyl*)-*ethane*-1 : 1-*dicarboxylates* (III); in the latter condensation it was found most convenient to use the modification of Albertson, Archer, and Suter (*J. Amer. Chem. Soc.*, 1945, **67**, 36), whereby the methosulphate of the gramine is made *in situ*, and essential to work in specially dried alcohol. In the one case in which it was investigated, *viz.*, the synthesis of 7-methyltryptophan, the use of acetamidocyanoacetic ester seemed to offer no advantages; Jackman and Archer (*ibid.*, 1946, **68**, 2105) have recently reported a synthesis of 5-methyltryptophan by this route. For the final stages the methods used by previous workers (direct acid hydrolysis and decarboxylation, or decarboxylation with boiling water followed by alkaline hydrolysis) proved inapplicable except in the case of the 7-methyl compound, owing to the great sensitivity of the methyl-substituted products towards acid. Success was finally achieved by hydrolysing the esters (III) to the *acids* (IV) with alkali, decarboxylating these by heating in nitrogen, and finally removing the acetyl group by alkaline hydrolysis. The overall yields (based on the methylindoles) and melting points of the methyltryptophans (V) prepared in the present work were as follows:

Substance.	Yield, %.	M. p.	
2-Methyltryptophan	46	234—235°	(Ellinger and Matsuoka, *Z. physiol. Chem.*, 1914, **91**, 45, record m. p. 234°)
4-*Methyltryptophan*	42	265—267	
5-Methyltryptophan	49	264	(Robson, *J. Biol. Chem.*, 1924, **62**, 495, records m. p. 259—263°, and Jackman and Archer, *loc. cit.*, m. p. 284—288°)
6-*Methyltryptophan*	56	258—260	
7-*Methyltryptophan*	65	296	

All these methyltryptophans, including the 2-methyl compound, gave intense colours in the formaldehyde reaction of Cole (S. W. Cole, " Practical Physiological Chemistry ", Heffer, Cambridge, 9th edition, 1933, p. 80); this was surprising, since Ellinger and Matsuoka (*loc. cit.*) state that 2-methyltryptophan gives a negative result in the glyoxylic acid test of Hopkins and Cole (*Proc. Roy. Soc.*, 1901, **68**, 21; *J. Physiol.*, 1901, **27**, 423) of which the formaldehyde reaction is supposed to be merely a modification. Accordingly, the colours given by the methyltryptophans in the best-known " aldehyde " reactions for tryptophan were investigated, with the results shown in the Table.

It is clear that Ellinger and Matsuoka's statement about the colour reactions of 2-methyltryptophan is correct; the Cole formaldehyde reaction now generally in vogue is more than a mere improved modification of the original Hopkins–Cole glyoxylic reaction, which was in general use some years ago, and confusion may arise in interpreting the earlier literature if this

	Colour and approximate position of maximum absorption in :			
	Adamkiewicz reaction.[2]	Hopkins–Cole glyoxylic reaction.[3]	Hopkins–Cole glyoxylic reaction with mercuric sulphate.[4]	Cole formaldehyde reaction.[5]
Tryptophan	Pale rose	Violet → blue. 5850 A.	Purple. 5640 A.	Violet → purple. 5680 A.
2-Methyltryptophan	Negative	Very faint blue-green on long standing.	Blue-green. General above 6500 A.	Blue-green. General above 6500 A.
4-Methyltryptophan	Pale rose	Grass-green → emerald. General below 4500 A.	Violet-blue. 5680 A.	Violet → blue. 5770 A.
5-Methyltryptophan	Rose → violet	Violet → blue. 5800 A.	Violet. 5620 A.	Blue → violet. 5650 A.
6-Methyltryptophan	Blue	Green → blue. 6000 A.	Blue. 5830 A.	Blue. 5850 A.
7-Methyltryptophan	Pale rose	Green → blue. 5850 A.	Violet-blue. 5650 A.	Blue. 5650 A.

[1] The details of the reactions are given in the experimental section.

[2] Reactions generally weak. The colours given by the 4- and the 5-methyl compound were by far the most intense.

[3] Stronger than (2) but less intense than (4) and (5). The 2-methyl compound gave only a trace of colour. The intensities of the colours given by the others was in the order 5-Me > 6-Me > 4-Me > 7-Me > tryptophan.

[4] Intense colours. Order : Tryptophan > 4- and 5-Me > 6- and 7-Me.

[5] Intense colours. 2-Me and 4-Me weakest.

is not borne in mind. It is clear from the Table that the two reactions give very similar results if both are carried out in the presence of mercuric sulphate, as always used in the Cole reaction; it seems probable that the modifying effect of mercuric sulphate is due to catalysis of further oxidation of the primary coloured products (cf. Mottram, *Biochem. J.*, 1913, **7**, 249), and it is noteworthy that copper salts have a similar action (Winkler, *Z. physiol. Chem.*, 1934, **228**, 50).

The present findings are in general agreement with the view of Fearon (*Biochem. J.*, 1920, **14**, 548) on the mechanism of these colour reactions, although the similarity of the colour reactions of 5-methyltryptophan to those of the 4-, 6- and 7-methyl compounds makes it clear that the condensation with formaldehyde to give the initial di-indolylmethane (" tryptophan red ") and bistetrahydrocarbolylmethane (" tryptophan blue ") colouring matters does not in every case involve only the C_7 positions of the indole nuclei as postulated by Fearon. The unique behaviour of 2-methyltryptophan is no doubt due to its inability to cyclise to a tetrahydrocarboline, in consequence of which it is able to give only a tryptophan red and not a tryptophan blue; it seems that the former is capable of giving rise to intense colours only in the presence of mercuric salts, as used in the Cole formaldehyde reaction but not in the Hopkins–Cole glyoxylic reaction.

Experimental.

Methylindoles (I).—2-Methylindole was prepared by the method of Fischer (" Beilstein ", 4th ed., **20**, 311) and 5-methylindole by Robson's method (*J. Biol. Chem.*, 1924, **62**, 495; cf. *Biochem. J.*, 1935, **29**, 557).

4-Methylindole. Crude, mainly 3-, nitro-*o*-xylene (111 g.; b. p. 95—114°/1·5 mm.) in alcohol (200 c.c.) was hydrogenated (*ca.* 5 atmos./room temp.) with 2% palladised strontium carbonate (5 g.). Distillation of the filtered product yielded 86·3 g. (91%) of mixed xylidines, b. p. 76—84°/1 mm. This mixture was heated under reflux on the water-bath for 3 hours with 90% formic acid (37 c.c.) and the product poured into water (120 c.c.); after being kept at 2° for 2 days the oily product partially crystallised and was then collected and drained on a porous tile. Crystallisation from 35% ethanol (charcoal) yielded pure *N*-formyl-2 : 3-dimethylaniline (29·6 g.; 28%), m. p. 100—102°.

This was added to warm *tert.*-butyl alcohol (200 c.c.) in which potassium (12 g.) had been dissolved, and the mixture heated in a metal-bath in a stream of dry nitrogen. *tert.*-Butyl alcohol distilled off at a bath temp. of 150—160°; decomposition of the residue set in at 340° and was completed by heating at 360° for 30 minutes; the distillate contained 6·7 g. of 2 : 3-dimethylaniline. The cooled residue in the reaction flask was treated with water and steam-distilled; the steam distillate was extracted with ether, washed successively with 2N-hydrochloric acid, water, 5% sodium carbonate, and water, dried and distilled, yielding 4-methylindole (5·7 g.; 44%), b. p. 110°/1 mm.; the picrate crystallised from benzene in red needles with a coppery reflex, m. p. 188° (Kruber, *Ber.*, 1929, **62**, 2877, records m. p. 194—195° and Marion and Oldfield, *loc. cit.*, m. p. 194°).

6-Methylindole. Two 30 g. batches of formyl-*p*-xylidine were cyclised as described for the 4-isomer. Distillation of the combined products yielded *6-methylindole* (13·1 g.; 50%) as an almost colourless oil, b. p. 111°/3 mm., which readily solidified, m.-p. 28° (Found : N, 11·3. C_9H_9N requires N, 10·7%); the *picrate* crystallised from benzene in felted orange-red needles, m. p. 152° (Found : C, 50·1; H, 3·4.

$C_{15}H_{12}O_7N_4$ requires C, 50·0; H, 3·3%). Marion and Oldfield (*loc. cit.*) give m. p. 161·5° for the picrate of an unanalysed specimen of 6-methylindole, prepared similarly, which showed no tendency to crystallise.

Methylgramines (II).—These were prepared by the following general procedure. Acetic acid (15 c.c.) was added slowly to 33% (*w/v*) aqueous dimethylamine (15 c.c.), cooled in a freezing mixture, at such a rate that the temperature did not rise above 5°; 40% formaldehyde solution (7·5 c.c.) was then added, the temperature being still kept below 5°. This solution was then poured on the methylindole (13·1 g.; 0·1 mol.) and the mixture shaken. The methylindole dissolved, with evolution of heat, in the course of a minute or two and the mixture was kept at room temperature for at least 4 hours; it was then poured into 2N-sodium hydroxide, and the solid methylgramine collected after the mixture had been kept overnight in the refrigerator. The following *methyl-3-dimethylaminomethylindoles* (II) were prepared in this way:

	Yield, %.[1]	Crystalline form.	M. p.	Found, %:[4] C.	H.
2-*Methyl-*	100	Feathery clusters of needles [2]	116—117°	76·4	8·5
4-*Methyl-*	97	Leaflets [3]	128—129	76·0	8·5
5-*Methyl-*	100	Acicular prisms [3]	133	76·1	8·2
6-*Methyl-*	99	Acicular prisms [2]	117	76·0	8·7
7-*Methyl-*	100	Needles [3]	114	76·2	8·6

[1] Yield of crude material sufficiently pure for use in the next stage.
[2] From dilute ethanol. [3] From dilute methanol. [4] $C_{12}H_{16}N_2$ requires C, 76·6; H, 8·5%.

Methyltryptophans (V).—The methylgramines were condensed with acetamidomalonic ester by the following procedure. The ester (21·7 g.; 0·1 mol.) and (crude) methylgramine (II) (18·8 g.; 0·1 mol.) were dissolved in alcoholic sodium ethoxide [from sodium (2·3 g.; 0·1 g.-atom) and magnesium-dried ethanol (250 c.c.)]; methyl sulphate (25·2 g.; 0·2 mol.) was added during 5—10 minutes, and the mixture kept at room temperature for 20—24 hours and then poured into water (1000 c.c.); the condensation product was precipitated, usually as a gum which crystallised on rubbing, and was collected after being kept in the refrigerator overnight. The crude product is very nearly pure and can be used directly for the next stage. Except in the 7-methyl series the use of less rigorously dried alcohol or heating the reaction mixture reduces the yield and leads to a less pure product. The following *ethyl* 1-*acetamido*-2-(x-*methyl*-3-*indolyl*)*ethane*-1 : 1-*dicarboxylates* (III) were prepared in this way:

x.	Yield, %.[1]	Crystalline form.[2]	M. p.	Found, %:[3] C.	H.
2-	80	Minute leaflets	170—171°	63·1	6·4
4-	82	Rectangular prisms	161	63·3	6·7
5-	85	Flat prisms	136	63·5	6·7
6-	79	Rosettes of small prisms	172—173	64·2	6·9
7-	93 [4]	Rosettes of acicular prisms	127	62·7	6·5

[1] Not recrystallised. [2] From dilute ethanol. [3] $C_{19}H_{24}O_5N_2$ requires C, 63·3; H, 6·7%.
[4] A 20% excess of sodium and acetamidomalonic ester was used, and the reaction mixture was refluxed for 3 hours after having been kept at room temperature for 3 hours.

The best procedures for the subsequent stages in the synthesis of the different methyltryptophans varied, and are therefore recorded in detail.

2-*Methyltryptophan*. The crude condensation product (III) (35·9 g.) was refluxed on the water-bath for 3 hours with sodium hydroxide (25 g.) in water (120 c.c.) and ethanol (240 c.c.). Alcohol was removed under reduced pressure, and water (240 c.c.) added to the residue; after being kept in the refrigerator for some hours, the yellow precipitate was filtered off and the filtrate extracted twice with *n*-butanol–chloroform (17 : 83 *v/v*). The aqueous layer was acidified with concentrated hydrochloric acid (63 c.c.) and shaken with 17% butanol–chloroform. A copious pale orange crystalline precipitate separated (it was sometimes necessary to keep the mixture overnight in the refrigerator) and was filtered off and dried in a vacuum desiccator; 24·2 g. (80%), m. p. 142°. Crystallisation from acetone–petroleum (b. p. 60—80°) yielded 1-*acetamido*-2-(2-*methyl*-3-*indolyl*)*ethane*-1 : 1-*dicarboxylic acid* (IV) in rosettes of acicular prisms, m. p. 143° (decomp.) (Found: C, 59·2; H, 6·0. $C_{15}H_{16}O_5N_2$ requires C, 59·2; H, 5·3%).

The unrecrystallised malonic acid (2·9 g.) was heated in an oil-bath at 180° for 20 minutes in a stream of dry nitrogen; after cooling in nitrogen, the residue was treated with a hot solution of barium hydroxide (6·0 g.) in water (20 c.c.) and the mixture heated at 100° for 26 hours with exclusion of atmospheric carbon dioxide. The solution was then freed completely from barium with the required amount of 2N-sulphuric acid, and the barium sulphate filtered off and washed well with three 20 c.c. lots of hot water. The filtrate and washings were evaporated under reduced pressure to 30 c.c., and alcohol (45 c.c.) added. A first crop of 2-methyltryptophan separated after being kept for some time in the refrigerator, and two further crops were obtained by evaporation and crystallisation of the solid residues from smaller volumes of 60% alcohol; in all 1·5 g. (72%) of crude material were so obtained. Two recrystallisations from 60% alcohol gave pure 2-methyltryptophan (V) (740 mg.) in small leaflets which, dried in a vacuum desiccator over phosphoric oxide for several days at 37°, had m. p. 234—235° after previous softening (Found: C, 65·6; H, 6·4. Calc. for $C_{12}H_{14}O_2N_2$: C, 66·1; H, 6·4%).

4-*Methyltryptophan*. The crude condensation product (III) (7 g.) was refluxed on the water-bath for 4 hours with sodium hydroxide (7 g.) in water (30 c.c.) and alcohol (45 c.c.). Alcohol was removed under reduced pressure and water (100 c.c.) added to the semi-solid residue. The product was filtered to remove a little insoluble material and the filtrate acidified with concentrated hydrochloric acid

(ice-cooling); the acidified solution was thoroughly extracted with ether and the dried extract evaporated, finally in a vacuum desiccator. The glassy product (4·6 g.) was crystallised from ethyl acetate–petroleum (b. p. 60—80°), yielding 4·4 g. (74%) of the malonic acid (IV), m. p. 117—119°. A further crystallisation from acetone–petroleum (b. p. 60—80°) yielded 1-*acetamido*-2-(4-*methyl*-3-*indolyl*)*ethane*-1 : 1-*dicarboxylic acid* in small needles, m. p. 131—132° (decomp.) (Found : C, 58·9; H, 6·1%).

The once-recrystallised malonic acid (IV) (4·4 g.) was heated in an oil-bath at 160° for 30 minutes in a stream of dry nitrogen. The cooled residue was then heated at 100° for 24 hours with barium hydroxide (10 g.) in water (40 c.c.), atmospheric carbon dioxide being excluded; boiling water (200 c.c.) was added to the product and barium removed completely with the requisite amount of 2N-sulphuric acid. The barium sulphate was filtered off and washed well with hot water; evaporation of the filtrate and washings to 150 c.c. under reduced pressure gave a first crop of 4-methyltryptophan (2·12 g.), and a further 0·12 g. was obtained by concentrating the mother liquors to 30 c.c. Crystallisation of these combined products (71% yield) from hot water (taken up in 350 c.c., boiled with charcoal, filtered, and concentrated to 150 c.c.) yielded 1·80 g. of 4-*methyltryptophan* (V) in small leaflets which, dried in a vacuum desiccator over phosphoric oxide, had m. p. 265—267° after softening from 250° (placed in bath at 240°) (Found : C, 66·2; H, 6·4%).

5-*Methyltryptophan*. The recrystallised condensation product (III) (8 g.) was hydrolysed as described for the 4-methyl isomer; the glassy product was crystallised from ethyl acetate–petroleum (b. p. 60—80°), yielding the malonic acid (IV) (6·5 g.; 96%), m. p. 119—121° (decomp.). A further crystallisation from the same mixture gave 1-*acetamido*-2-(5-*methyl*-3-*indolyl*)*ethane*-1 : 1-*dicarboxylic acid* in small prismatic needles, m. p. 129° (decomp.) (Found : C, 58·6; H, 5·2%).

The once-recrystallised malonic acid (IV) (5 g.) was decarboxylated and hydrolysed as described for the 4-methyl compound; evaporation of the barium-free solution to 100 c.c. gave a first crop (1·79 g.) of 5-methyltryptophan, and a further 0·35 g. was obtained by concentrating the mother-liquors (total yield : 2·14 g.; 60%). Recrystallisation from hot water (dissolved in 200 c.c., boiled with charcoal, filtered, and concentrated to 90 c.c.) yielded 5-methyltryptophan (V) in leaflets, m. p. 264° (decomp.) after softening from 245° (Found : C, 65·7; H, 6·6%).

6-*Methyltryptophan*. The recrystallised condensation product (III) (12 g.) was hydrolysed as described for the 4-methyl compound; the glassy product (10 g.; 99%) was crystallised from ethyl acetate–petroleum (b. p. 60—80°), yielding 1-*acetamido*-2-(6-*methyl*-3-*indolyl*)*ethane*-1 : 1-*dicarboxylic acid* (IV) in rosettes of stout needles, m. p. 130—132° (Found : C, 58·8; H, 6·1%).

Hydrolysis with barium hydroxide was unsatisfactory owing to the low solubility of the barium salt of 6-methyltryptophan. Accordingly, the crude malonic acid (IV) (2·5 g.) was decarboxylated as usual and then heated at 100° for 23 hours with a solution of potassium hydroxide (2·0 g.) in water (25 c.c.). Water (10 c.c.) and acetic acid (2·05 c.c.) were added to the hot solution which was then left to crystallise in the refrigerator overnight. The crude 6-methyltryptophan (1·30 g.; 73%) was filtered off, washed, and dried in a vacuum desiccator. Recrystallisation from hot water (charcoal) yielded 6-*methyltryptophan* (V) (0·75 g.) in small shining leaflets, m. p. 258—260° after softening from 245° (Found : C, 66·1; H, 6·2%).

7-*Methyltryptophan*. The crude condensation product (III) (10 g.) was refluxed for 3 hours with sodium hydroxide (8 g.) in water (50 c.c.) and alcohol (100 c.c.). Alcohol was removed under reduced pressure, and the residue treated with water (50 c.c.) and concentrated hydrochloric acid (50 c.c.) and refluxed for 3 hours. After filtration from a little tar, the solution was brought to pH 5—6 with 2N-sodium hydroxide and rapidly filtered from an immediate dirty precipitate. The white solid deposited after the solution had been seeded and kept overnight was filtered off and dried in a vacuum desiccator (6·0 g.; 99%). Recrystallisation from water (dissolved in 1000 c.c., boiled with charcoal, filtered, and concentrated to 300 c.c.) yielded 3·5 g. of fairly pure 7-methyltryptophan, m. p. 283—285° (decomp.), a further 0·75 g. being obtained by concentrating the mother liquors to 100 c.c. For final purification, 6·0 g. of such material was dissolved in N-hydrochloric acid (120 c.c.) and extracted 5 times with *n*-butanol–chloroform (17 : 83 *v/v*). The residual aqueous solution was filtered through a wet paper, and 2N-sodium hydroxide (60 c.c.) added; the methyltryptophan (3·0 g.) crystallised in rosettes of pointed needles. Recrystallisation from water yielded 2·35 g. of pure 7-*methyltryptophan* (V) in small leaflets, decomp. 296° after softening from 264° (Found : C, 66·3; H, 6·6%). 7-Methyltryptophan (200 mg.) was dissolved in 2N-sodium hydroxide (2·0 c.c.) and treated with six 0·1 c.c. lots of acetic anhydride, the mixture being shaken well after each addition; the product was kept at 37° for 2 hours and then at 0° overnight. The solid (200 mg.; 83%) was filtered off, washed with water, and crystallised from water; N-*acetyl*-7-*methyltryptophan* formed feathery aggregates of needles, m. p. 217—218° (Found : C, 64·1; H, 6·4. $C_{14}H_{16}O_3N_2$ requires C, 64·6; H, 6·1%).

In another series of experiments, acetamidocyanoacetic ester (2·9 g.) and 7-methylgramine (II) (3·2 g.) were added to alcoholic sodium ethoxide [from sodium (0·40 g.) and absolute alcohol (25 c.c.)]. The mixture was refluxed on the water-bath while a mixture of ethyl iodide (2·66 g.) and absolute alcohol (10 c.c.) was added during 15 minutes. The mixture was refluxed for 22 hours and the alcohol removed under reduced pressure. The residue was treated with water and extracted with chloroform; evaporation of the dried chloroform extract, washed with 2N-hydrochloric acid, 10% sodium hydrogen carbonate, and water, yielded 3·55 g. (67%) of a glass; crystallisation from dilute ethanol gave *ethyl* 1-*acetamido*-1-*cyano*-2-(7-*methyl*-3-*indolyl*)*ethane*-1-*carboxylate* in small prisms, m. p. 183° (Found : C, 65·6; H, 6·5. $C_{18}H_{19}O_3N_3$ requires C, 65·2; H, 6·1%). This crude condensation product (3·3 g.) was refluxed for 19 hours with potassium hydroxide (3·1 g.) in water (10 c.c.) and alcohol (10 c.c.). After distillation of the alcohol, water was added to bring the volume to 50 c.c., and a precipitate removed. The filtrate was treated with 2N-hydrochloric acid to maximum precipitation and then kept in the refrigerator overnight. The solid (1·54 g.) was filtered off and refluxed for 3 hours with water (15 c.c.), some tar and 7-methylindole being formed; sodium hydroxide (1·2 g.) was added and refluxing continued for 19 hours. Water (10 c.c.) was added, and the solution filtered; addition of acetic acid (1·72 c.c.) precipitated crude 7-methyltryptophan (1·2 g.; 52%) which was filtered off, dissolved in water (20 c.c.) containing

sodium hydroxide (0·75 g.), boiled with charcoal, filtered, and reprecipitated by adding alcohol (10 c.c.) and acetic acid (1·12 c.c.). After the mixture had been kept in the refrigerator overnight the precipitate (780 mg.) was filtered off and recrystallised from boiling water, yielding pure 7-methyltryptophan in small shining leaflets, decomp. 296° after softening from 264°.

Colour Reactions of the Methyltryptophans.—The reactions were carried out as follows, the absorption bands being observed with a Hartridge reversion spectroscope after dilution, if necessary, with 50% *v/v* sulphuric acid.

(A) *Adamkiewicz reaction* (*Pfluger's Arch.*, 1874, **9**, 156). 1 C.c. of a solution of the methyltryptophan (1 mg./c.c.) was mixed with 1 c.c. of glacial acetic acid, underlayered with 2 c.c. of concentrated sulphuric acid, and finally mixed.

(B) *Hopkins–Cole glyoxylic reaction* (S. W. Cole, *op. cit.*, p. 39). 1 C.c. of a solution of the methyltryptophan (1 mg./c.c.) was mixed with 1 c.c. of the "glyoxylic reagent", underlayered with 2 c.c. of "AnalaR" sulphuric acid, and finally mixed.

(C) *Hopkins–Cole glyoxylic reaction with mercuric sulphate.* As (B) but with addition of 2 drops of the mercuric sulphate used in (D).

(D) *Cole formaldehyde reaction* (S. W. Cole, *op. cit.*, p. 80). 1 C.c. of a solution of the methyltryptophan (1 mg./c.c.) was mixed with 1 c.c. of water, 2 drops of 1/500 formalin, and 2 drops of 10% mercuric sulphate in 10% sulphuric acid, underlayered with 2 c.c. of "AnalaR" sulphuric acid, and finally mixed.

I am much indebted to Miss B. W. Boughton for skilled technical assistance and to Dr. F. Bergel, of Roche Products Ltd., for generous gifts of nitro-*o*-xylene. Micro-analyses were carried out by Drs. G. Weiler and F. B. Strauss of Oxford.

MEDICAL RESEARCH COUNCIL UNIT FOR BACTERIAL CHEMISTRY,
LISTER INSTITUTE, LONDON, S.W.1. [*Received, May* 31*st*, 1947.]

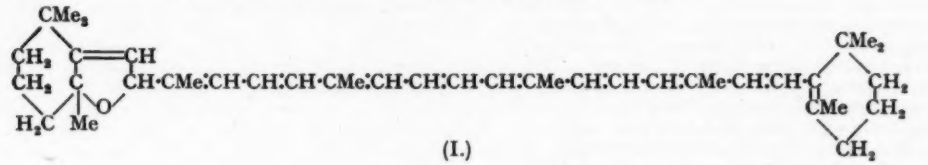
NOTE.

X-*Ray Investigation of Some Oxidation Products of β-Carotene.* By R. F. HUNTER, T. R. LOMER, V. VAND, and N. E. WILLIAMS

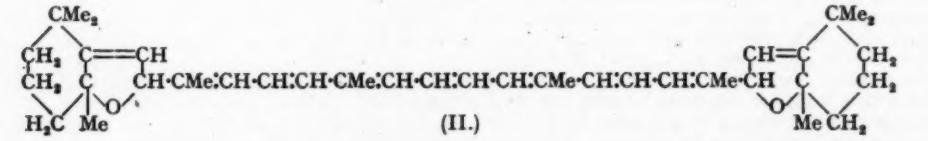
IT appeared desirable to supplement the chemical and spectroscopic evidence of structure of the crystalline products formed in the study of oxidation of β-carotene by oxygen (Hunter and Krakenberger, *J.*, 1947, 1) by *X*-ray measurements on carefully purified specimens of the carotenoids prepared by methods given in the literature. It also appeared probable that such data would enable us to obtain some information with regard to oxidation in the crystalline state.

The unit cell for β-carotene was determined by Taylor (*Z. Krist.*, 1937, **96**, 150) from single crystal measurements, who showed that it has a monoclinic cell of $a = 7{\cdot}75$, $b = 9{\cdot}5$, and $c = 25{\cdot}0$ A., $\beta = 105°$, containing two molecules per unit cell at co-ordinates 0,0,0, and $0,\frac{1}{2},\frac{1}{2}$, the space group being $C_{2h}^5 - P2_1/c$.

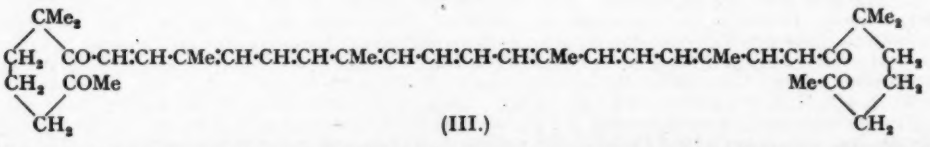
X-Ray diffraction data are now reported for all-*trans*-β-carotene, mutatochrome (I) (formerly regarded as "β-carotene oxide", Karrer and Jucker, *Helv. Chim. Acta*, 1945, **28**, 427), aurochrome to which Karrer and Jucker have assigned the formula (II), and β-carotenone (III).



(I.)



(II.)



(III.)

No crystals large enough for a complete *X*-ray analysis by a single crystal method could be obtained. However, as the unit cell of β-carotene was already known, and as the powder patterns of its oxidation products are closely related, it was possible to index the diffraction lines on their powder photographs and so deduce the probable unit cells of the compounds studied, under the assumption that their unit cells do not differ greatly from that of β-carotene. A graphical method of indexing the powder photo-

graphs, which will be described elsewhere, has been used. As the resolving power of our powder camera is relatively high, it has been possible to determine the unit cell of β-carotene from the powder photographs more accurately; the unit cell so determined agrees well with that of Taylor.

The dimensions of the resulting unit cells in kX are given in the Table I.

TABLE I.

Compound.	*a*.	*b*.	*c*.	β.	Density: calc. from *X*-ray.	Density: observed (flotation).
β-Carotene	7·745	9·44	25·2	105·5°	1·00	—
Mutatochrome	7·75	9·66	25·2	105·0	0·998	—
Aurochrome	7·64	9·90	26·1	106·5	0·992	0·996
β-Carotenone	7·55	9·31	25·0	105·0	1·16	1·16

The dimensions of the unit cells chosen account for practically all of the observed diffraction lines and for the density, assuming two molecules per unit cell. As, however, the determination of the unit cell from the powder photographs is not as certain as from single crystals, and the determination of the space group is impossible, the data must not be regarded as final. Since β-carotene has a centre of symmetry and mutatochrome (I) cannot have one, it is quite probable that the true unit cells of some compounds are multiples of ours, requiring thus a doubling of one or more of our cell edges. The observed lines are described, however, in terms of the unit cells given.

The results show that on passing from β-carotene to mutatochrome the *b* cell edge increases by 0·22 kX, whereas the other parameters remain practically constant. Similarly, on passing from mutatochrome to aurochrome, the *b* cell edge increases by a further 0·24 kX, whereas the remaining parameters show only small changes. This progressive change of the *b* cell edge can be understood from the chemical evidence; the nuclear oxygen atoms evidently distend the cell dimensions in the direction of the *b* axis, and their action is therefore additive. On the other hand, β-carotenone shows a significant shrinkage in both *a* and *b* cell edges, accompanied by an increase of density. This can be understood from the effect of coiling back of the opened terminal ionone rings.

Interesting qualitative information with regard to oxidation of β-carotene, aurochrome, and β-carotenone by air in the solid crystalline state was obtained by re-examining the specimens which had been kept in the specimen holders at laboratory temperature for periods of 20 days and 3 months. No detectable change in the *X*-ray pattern of β-carotene was observed after 20 days; considerable weakening of the pattern occurred, without appearance of new lines, after 3 months. A similar result, but with less weakening of the pattern after 3 months was observed with aurochrome; again, no new lines were observed indicating the amorphous nature of the oxidation product. With β-carotenone, however, the pattern remained unchanged during the period of 3 months, indicating the higher stability of this carotenoid.

Experimental.—The specimen of β-carotene was freshly recrystallised and stored in carbon dioxide before measurement ($E^{1\%}_{1\,cm.}$ = 2300 at 464 mμ. in benzene).

The specimen of mutatochrome was one of those prepared by oxidation of β-carotene with perbenzoic acid and purified by rechromatography and recrystallisation as already described (Gridgeman, Hunter, and Williams, *J.*, 1947, 131).

Aurochrome, prepared by oxidation of β-carotene with perbenzoic acid and purified by rechromatography and recrystallisation from acetone, had m. p. 184° (abs. max. at 456 and 429 mμ. in carbon disulphide).

β-Carotenone was prepared by Kuhn and Brockmann's method (*Ber.*, 1932, **65**, 894). The recrystallised specimen showed absorption maxima at 538·5, 502, and 470 mμ, in carbon disulphide.

The powder photographs were taken with Ni-filtered Cu-K_α radiation in our 12·5 cm. focusing camera of the Frevel type, which will be described elsewhere. As a source of *X*-rays, a Metrovick "Raymax" demountable tube with aluminium windows was used. The exposures were for 1½ hours at 46 kv. and 20 ma. The specimens were sealed in specimen holders between two single cellophane sheets by means of a pressure-sensitive adhesive, and the first series of photographs taken immediately after sealing. The thickness of the specimens was arranged to be equal to the reciprocal value of the linear absorption coefficient of the specimen.

TABLE II.

d.	Intensity.	Index.	$d_{calc.}$	*d*.	Intensity.	Index.	$d_{calc.}$
			β-Carotene.				
8·870	2	011	8·80	3·534	10	$21\bar{3}$	3·525
7·536	10	100	7·47	3·371	10	—	—
6·075	80	013—80% 004—20%	6·14 6·07	3·234	10	—	—
				3·081	5	026	3·073
5·708	60	102	5·72	2·966	5	213	2·944
5·492	10	111	5·48	2·857	8	—	—
5·324	80	$11\bar{3}$	5·30	2·747	2	$20\bar{8}$	2·741
5·050	10	014	5·108	2·621	1	—	—
4·722	100	$11\bar{4}$	4·742	2·528	2	—	—
4·442	10	022	4·399	2·481	2	—	—
4·165	50	104—50% $11\bar{5}$—50%	4·194 4·194	2·436	1	206	2·439
				2·358	1	—	—
4·055	50	023	4·078	2·319	1	—	—
3·843	10	—	—	2·274	1	—	—
3·640	90	016—95% $20\bar{4}$— 5%	3·720 3·623	2·182	2	—	—
				2·030	5	—	—

TABLE II—*continued.*

d.	Intensity.	Probable index.	$d_{calc.}$.	*d*.	Intensity.	Probable index.	$d_{calc.}$.
			Mutatochrome.				
7·645	2	012	7·57	4·324	8	015	4·355
7·153	20	$10\bar{2}$	7·27	4·165	15	—	—
6·720	10	101	6·685	3·679	60	—	—
6·090	40	004	6·086	3·448	10	—	—
5·906	30	110	5·917	3·173	5	—	—
5·708	10	102	5·747	2·950	1	—	—
5·261	80	$11\bar{3}$	5·329	2·255	2	—	—
5·076	20	$\frac{1}{2}0\bar{5}$	5·076	2·020	2	—	—
4·831	100	020	4·831	1·852	1	—	—
4·480	5	022	4·491				
			Aurochrome.				
8·34	60	003	8·32	3·478	1	025	3·515
6·25	5	004	6·24	3·360	1	—	—
6·00	10	$11\bar{1}$	6·038	3·146	5D	—	—
5·557	100	102	5·643	3·096	2D	—	—
5·282	10	014	5·280	3·03—2·97	2D	—	—
5·158	10	?	?	2·902	1	—	—
4·842	20	103, 021	4·847, 4·854	2·82—2·72	2D	—	—
4·588	5	022	4·602	2·570	1	—	—
4·241	20	023	4·255	2·438	1	—	—
4·039	10	120	4·102	2·343	1	—	—
3·880	2	024	3·877	2·227	1	—	—
3·784	1	$20\bar{2}$, $20\bar{1}$	3·808, 3·771	2·110	1D	—	—
3·713	2	122	3·713	2·033	1	—	—
3·614	20	105, 200	3·665, 3·652	1·869	1	—	—
			β-Carotenone.				
7·94	1	003	8·05	3·279	1	—	—
7·17	25	$10\bar{2}$	7·11	3·185	1	—	—
6·41	1	101, $10\bar{3}$	6·53, 6·27	3·140	1	—	—
6·06	2	013, 004	6·09, 6·04	3·048	3	—	—
5·751	25	110	5·741	2·976	5	—	—
5·391	15	$10\bar{4}$	5·382	2·931	1	—	—
5·102	4	014	5·066	2·819	2	—	—
4·975	5	?	?	2·780	2	—	—
4·842	100	103, 112	4·819, 4·819	2·703	1	—	—
4·658	50	020, $11\bar{4}$	4·656, 4·660	2·621	2	—	—
4·386	1	022	4·344	2·570	2	—	—
4·292	15	113	4·281	2·506	1	—	—
4·207	8	104	4·155	2·342	1	—	—
4·122	40	$11\bar{5}$	4·132	2·268	1	—	—
3·877	3	$12\bar{2}$	3·894	2·152	1	—	—
3·731	3	$12\bar{3}$	3·737	2·106	1	—	—
3·656	10	$11\bar{6}$	3·664	2·020	2	—	—
3·460	15	201	3·476	1·987	2	—	—
3·368	8	—	—	1·802	2	—	—

In Table II are given the values of the observed spacings *d* in kX, the relative intensities of the diffraction lines, their probable indices, and the spacings calculated from the assumed cells. The relative intensities * were estimated by eye, taking the intensity of the strongest line as 100.

We thank the directors of Lever Brothers and Unilever Ltd. for permission to publish these results.—
RESEARCH DEPARTMENT, LEVER BROTHERS AND UNILEVER LTD., PORT SUNLIGHT. [*Received, March 4th*, 1947.]

* According to our experience, the intensities obtained with our camera are comparable with the intensities obtained with cameras usually used.

The Hopkins Memorial Lecture.

DELIVERED BEFORE THE CHEMICAL SOCIETY ON FEBRUARY 19TH, 1948.

By SIR EDWARD MELLANBY, G.B.E., K.C.B., M.D., F.R.S.

WHILE I feel greatly honoured in finding myself in the position to-night of giving a memorial lecture to Sir Frederick Gowland Hopkins, I am conscious that this is a challenge and an opportunity which demand qualities to which I can make no special claim. A man who can be regarded as one of the greatest scientists and, in his own sphere, the greatest scientist of his time, is very rare. A man who is esteemed by everybody and regarded with affection by all his friends, colleagues, and pupils, is by no means common. The combination of both these qualities in one person presents us with a man of such outstanding individuality that the degree of knowledge, skill, judgment, and sympathy required to give his bibliographic lecture is almost unattainable. I can only promise to do my best.

Most of this lecture will be taken up by an account of Hopkins's scientific work, but before beginning this subject I should like to place on record some of his personal qualities, although I imagine that many here are familiar with these. Indeed, one of the thoughts that first passed through my mind in preparing this lecture was the large number of men who could with more justification be called upon to give it.

There are few men with whom one would rather have had a personal chat than Hopkins. This was because, in all conversation, he was kind, unselfish, gentle, sympathetic, and thoughtful, and yet a man of great sense and knowledge. He had a remarkable power of sending a man away much happier than when he came, and, if the subject of discussion was one of scientific research, especially after some depressing experience, a man was much more prepared to carry on with his labours and forget his trouble. This was certainly my experience and must have been common to most other men who had the good fortune to be associated with him in the laboratory. Hopkins had a great stimulating power on young people. A particular instance of this kind happened at an early stage of my undergraduate career at Cambridge, when he introduced to a class taking the Tripos in physiology a discussion on the volume of blood in the body. He succeeded in rousing in me a state of enthusiasm sufficient to make me confine my whole attention to this problem for a fortnight to the detriment of my other work, in order to find a method to decide whether the blood volume was one-thirteenth or one-twentieth of the total body weight. This was an exaggerated reaction of the kind with which I was constantly affected in the few years in which I was intimately associated with him in the laboratory. So long as Hopkins had a small class or a small audience, he had this same power of making them feel pleased with themselves and sending them away happy. With large audiences these qualities were not apparent, because of the smallness of his voice. A good instance of Hopkins's method of talking, either to individuals or to small groups, can be seen in the opening words of a lecture he gave to the Public Analysts of the country in 1906, a discourse which has often been quoted, since in it he outlined the discovery of what came to be known as vitamins. Everybody knows that he had been trained as a chemical analyst and that later he had medically qualified, and that in the year 1906 he was already a Fellow of the Royal Society and a man of real distinction, lecturing before a group of people who were, for the most part, ordinary analysts and medical men. He began this lecture with the words: "Seldom I imagine has this learned society welcomed a visitor less obviously entitled to occupy its time." He then proceeded: "I came to the conclusion that the only real qualifications I had for coming before you were those possessed by an individual who, having been trained for your own profession and having acquired some knowledge of its aims and claims, sought later a training in the profession of medicine and so gained similar knowledge with regard to it. I am, of course, very far from standing alone in this experience but, unlike many who, with the same double training, have practised one or other of these professions with distinction, and still more unlike those who have contrived to practise both, it has been my fate never at any time to practise either." Hopkins, in these few words, stated the exact position but stated it so modestly that most people in the room must have had a feeling of superiority, and yet at that time he had gone a long way to having demonstrated that he was a combination of the ablest analyst and the ablest medical man in the country.

I have thought it well to say these few words of introduction about Hopkins, because nobody could fail to appreciate these remarkable qualities, which were present even when he had reached the highest point of activity and also of fame.

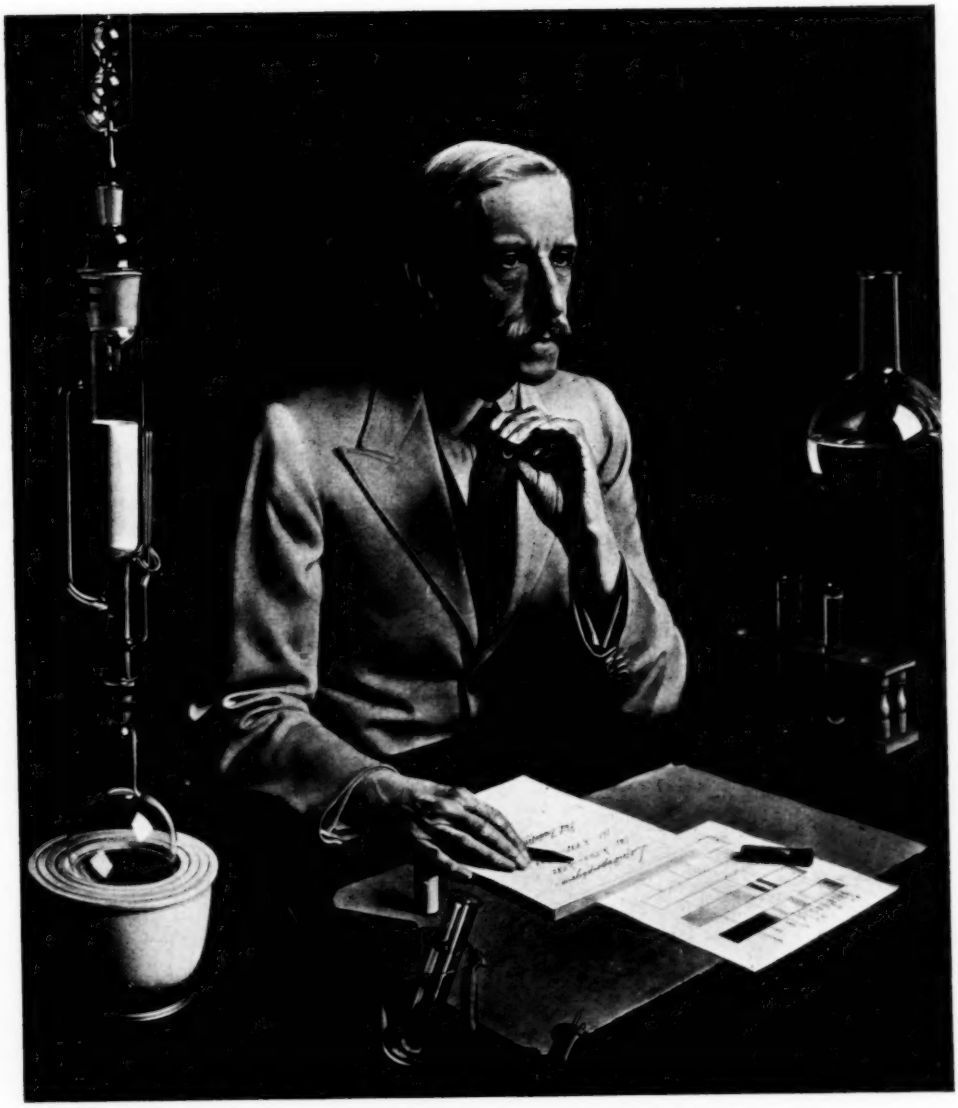
Before discussing Hopkins's scientific research, I wish briefly to refer to those parts of his history which bear upon this work. He was born in 1861, and at the age of 17 was articled to a public analyst, from whom he received his first technical training. In 1883, at the age of 22, he was appointed assistant to Sir Thomas Stevenson, the Home Office Analyst, with whom he stayed for about five years. Then at the age of 27 he became a medical student at Guy's Hospital, and he graduated at the University of London in both science and medicine in 1894. In 1898, when Hopkins was 37, Sir Michael Foster invited him to join the Physiological Department at Cambridge as a University Lecturer, in order to develop the subject of chemical physiology. From 1905 to 1910 he was tutor of Emmanuel College. While he was now in a better financial position, his duties as a college tutor and university lecturer were exacting and must have interfered with his research. In 1910 his pleasure was great when Trinity College offered him a fellowship and appointed him Praelector in Physiological Chemistry, so that he became free from all routine teaching work. In the following year he was made university reader in chemical physiology. In 1914 a special chair of biochemistry was created for him, and a separate biochemical department was formed. In 1921 a large bequest from the Trustees of Sir William Dunn made it possible to provide him with a separate building and staff for the new department. This building was completed and occupied in 1924, and Hopkins immediately started work with a large research staff (of about forty) in this year. It is worthy of mention that before Hopkins got a proper university laboratory and department at Cambridge he had arrived at the age of 63. He continued as professor of biochemistry until 1943, and retired after having held the chair for thirty years. The points, I think, to remember in Hopkins's earlier career are first, that there was practically nothing academic about his original training, except the medical course at Guy's Hospital, and secondly, the great preparation he underwent in first learning the profession of chemical analyst and then following this up by becoming medically qualified. Little wonder that he did not get properly going in his research life until he was approaching the age of 40. On the other hand, it is equally without wonder that a man of his mental calibre and other intellectual qualities having had such a magnificent training should have proved to be one of the most outstanding scientists the country has ever seen.

Hopkins's first entry into the field of research occurred at the age of 17, when he sent the following note to *The Entomologist* for November 1878:

> "*Brachinus crepitans*.—I have observed that the little bombardier beetle has been exceedingly plentiful this year, and I feel interested to know if this has been the experience of others. I caught my first specimen in March, and this was the first I had ever seen here; since then, and till quite lately, they have appeared in great numbers. On the South Downs, near Eastbourne, I also saw several of these insects, though I have no recollection of having observed them there before. Altogether *Brachinus* seems to have been an exception to the general scarcity of his order this year. It is a very sociable insect, and I have seldom seen one without finding others close by. The beetles are very partial to my sugar compound, and have swarmed on trees prepared for moths. *Colias edusa* has quite disappeared from here this year.—F. G. Hopkins."

Fifty-seven years later the *London Naturalist* for 1935 contains the address that Hopkins gave on his election as Honorary President of the London Natural History Society in succession to Lord Grey of Fallodon. In the course of this address he refers again to his original observations on *Brachinus crepitans*:

> "I will here venture, hoping for your forbearance, to intrude a fragment of personal history into my remarks. Like Bacot himself and, I suspect, like very many of my audience, I was in my early days an ardent collector of butterflies and moths and (next easiest, I think, for the boy or amateur) of beetles. It was one day in March of the year 1878—it is just 57 years ago—that I first made, with infinite pleasure, the acquaintance of the little bombardier beetle, *Brachinus crepitans*, if that be still its accepted scientific designation. It was plentiful that year and I found it in a northern suburb of London and on the South Downs near Eastbourne. Now, when one day I beheld, without previous knowledge of their abilities, how these insects on being disturbed eject a violet vapour into the air, a most effective act for offence or defence, I felt an intense curiosity to know not only how this volatile stuff could be made and stored but in particular what the stuff could be. I tried a few experiments, putting one bombardier after another into the same test tube, and encouraging each one to shoot. The vapour condensed on the side of the covered tube and I thus collected a little of the material. It was very little, however, and I was a youth



SIR FREDERICK GOWLAND HOPKINS.

[*To face p.* 714.

with no chemical training, so nothing came of my researches. I think, however, that from that time my fate was sealed. Though the designation was not yet invented, I became there and then a biochemist at heart."

Hopkins's next contribution came only after a gap of eleven years, namely in 1889, and, again, the subject concerned insects. He was now able to bring the specialist technique of the analyst to bear on the chemistry of the pigments of butterflies' wings. In the particular case he found that the yellow pigment present in the common English brimstone butterfly could be obtained in solution by simple treatment with hot water. It was not until 1896, however, that research on this subject was fully published by Hopkins in the *Philosophical Transactions of the Royal Society* under the title " Pigments of Pieridæ." It will be remembered that the results of this work were to show that the opaque white substance in the wings of Pieridæ is uric acid, while in the yellow insects the pigment is a related substance, probably identical with one obtained when uric acid is heated with water under pressure, the mycomelic acid of Hlasiwetz. In this work it is possible to see an example of what was a constant occurrence in all Hopkins's publications, namely the establishment not only of a fact or series of facts but also of some idea or suggestion which gave such facts a much wider interest and interpretation. In this particular case he dwells on the fact that in these coloured insects as well as in the white insects the pigmentary substance is actually excreted and that these are examples of normal excretory products being made to subserve the purposes of ornament.

It is a remarkable fact that in 1941, fifty-two years after his first publication on the chemistry of butterfly pigments, Hopkins published another paper on this subject entitled " A Contribution to the Chemistry of Pterins." He was constrained to return to this problem by the fact that Wieland and his colleagues had shown in a series of papers from 1925 to 1940 that these pigments were not uric acid derivatives but belonged to a new group of compounds known as pterins. There is some similarity between pterins and purines, in both their chemical constitution and properties. In recent years the pterins have become substances of great biological interest, one of the most important observations being that a pterin group is found in the folic acid molecule.

Hopkins's work on the chemistry of the pigments of butterfly wings caused him to extend his interest to uric acid problems in man, and in 1893 he published two papers describing a new method of determining uric acid in urine. Whatever developments may have taken place in methods of determining uric acid in later days, I can only say that Hopkins's method was in extensive use for many years after its discovery. This interest in the part played by uric acid in human metabolism he maintained for a good many years, and, even as late as 1898 and 1899, we find him publishing papers on the relation of uric acid excretion to diet. It may be added that all this work was a reflection of the great medical and public interest taken at that time in gout and its relation to uric acid formation. With the decline in incidence and indeed with the practical disappearance of gout from the country, the interest in uric acid has never again been so intense, although the mystery of the disease is still as great as ever.

During his time at Guy's Hospital he also produced a number of other papers, to which I shall just refer in passing, besides the one on the pigments of the Pieridæ and the uric acid publications. With Garrod he published a note on the excretion of hæmatoporphyrin in the urine of patients taking sulphonal, and two papers on urobilin. At this time, also, another chemical problem became apparent in his publications, namely the study of halogen derivatives of proteins. I shall not dwell on this work except to mention that one of these observations—the interaction of bromine with protein—became a further interest in his later work when isolating the amino-acid, tryptophan.

I have mentioned this series of publications for which Hopkins was responsible during the period of his medical qualification and of his early medical years, *i.e.* 1889—1898, in order to show that, although he continued in vigorous research activity and although his work still retained a certain distinctive superiority, it is perhaps questionable whether, if he had remained in this environment, his research would have reached the same high-water mark as in fact it did after he arrived at Cambridge. My own view is that the best thing that happened to Hopkins, both from his own standpoint and from that of the scientific world, was his departure from the medical atmosphere of Guy's Hospital in 1898 to the Physiology Laboratory at Cambridge. Cambridge, and especially that Laboratory, had a great deal to give as well as to receive.

Hopkins had not been long in Cambridge when he got the stimulus which led to his first research of classical importance and which, indeed, brought him at one stride to the forefront of physiological chemists. In a Part II practical class in physiology, one of the tests made by

the students was that known as the Adamkiewicz colour reaction for proteins (proteids, as they were called in those days). Hopkins was scornfully reminded by the class that this test was useless, as indeed it was in this instance, and he felt impelled to find out the cause of failure. It will be remembered that he soon found that the colour reaction was not due to acetic acid itself but to an impurity, glyoxylic acid, and the test is now called the glyoxylic test for protein.

He then proceeded with the assistance of Sydney Cole to apply his supreme analytical skill to discover what exactly it was in protein that gave the purple reaction with glyoxylic acid. Hopkins was always happy with a colour test when on the scent, and, indeed, if there were no colour test at hand, he usually proceeded to discover one. With the aid of the glyoxylic test he and Cole soon found the right reagent, namely mercuric sulphate in dilute sulphuric acid, for precipitating tryptophan from protein digests and separating it from the other amino-acids. The decision that this substance was the hypothetical compound tryptophan, which reacted with bromine water to give a rose-red colour, was an interesting and most important chapter of this work. (It will be remembered that Hopkins and Cole thought at first that this substance was skatoleaminoacetic acid and that it later turned out to be indoleaminopropionic acid.)

It is characteristic of Hopkins that he did not rest after this chemical triumph or simply pass on to another subject. His mind was characteristically directed at once to the meaning of this new chemical grouping in protein, and he wanted to know if it had some special duty to perform in the animal economy. With Edith Willcock, later Mrs. Stanley Gardner, he proceeded to do feeding experiments on young mice with synthetic diets of pure substances, and, by using zein made from maize as the sole source of protein, he obtained a tryptophan-free diet. Control mice he left on this diet and to the diet of other mice he added either tyrosine or tryptophan. Thus evidence was obtained that, although the tryptophan did not make these mice grow, it added considerably to their length of life and obviously played an important nutritional rôle in animal metabolism. This was one of the earliest experiments (1907) directed to showing the importance of quality of diet, and it formed one of the essential classical tests which brought this aspect of nutrition to the great prominence of later years.

One of the most important investigations in which Hopkins participated was that into the part played by lactic acid in muscle metabolism. This work was done in 1905—1907, and at this period I was closely associated with Hopkins and, indeed, shared with him the small room in which it was done. It will be remembered that W. M. Fletcher, who had previously worked on lactic acid in muscle, collaborated with Hopkins, and in my view he was responsible for inducing him to join in this further investigation. It would be wrong, however, if I left the impression that Fletcher was the major partner in this work. This was certainly not so, and I am quite sure that, not only as regards the ideas and philosophy behind the work but also as regards the actual labour involved in the investigation, Hopkins more than played his part. Many people would perhaps consider that this particular research of Hopkins did not occupy the major position in his scientific history that I consider is its due. It is true that, unlike most of his other work which was nearly always that of breaking new ground, this investigation on lactic acid was rather of the nature of development of a recognised problem. It was known or at least stated that lactic acid appeared in muscle under various conditions of activity, but the whole subject was a medley of contradiction. The merit of the Fletcher and Hopkins investigation was not only that, by careful, quantitative work, order was brought out of chaos, but, more important still, that the results were of such great interest and the issues, especially as set out in the publication, so important that they stimulated all manner of further research on muscle physiology, biochemistry, and biophysics, which continued for many years.

You may remember that one of the great difficulties met with early in this work was that, not only when muscle was stimulated to activity but even when it was treated in any way, mechanical or chemical, it responded by producing lactic acid. Nursing muscle by rest, and especially pampering it by surrounding it at the same time with an atmosphere of pure oxygen, caused the lactic acid to disappear or to be greatly reduced, but both the appearance and disappearance of this substance depended upon the tissue cells being alive. Thus Hopkins in this research was dealing with a chemical problem of actual living tissue, and it was this experience (the only one of its kind in his career, so far as I can remember) which helped him on to the road of what became his later, greatest interest—the chemical dynamics of the living cell.

The first problem in this work was to obtain lactic acid out of resting muscle without getting the back-kick of further production—a reaction which had spoiled much previous work on the subject. This was done by rapidly freezing and grinding the dissected muscle in cold alcohol which dissolved out the lactic acid present. It is unnecessary to give the detailed results of this work, but it may be useful to point out that the actual attempt that Fletcher and Hopkins

made to explain these strange results in terms of muscle function and metabolism as understood at that time is an interesting chapter in physiological chemistry. It was obviously impossible for them to make a serious interpretation of the results without a much fuller knowledge of other simultaneous chemical and physical changes of muscle, such as its glycogen content, oxygen intake, carbon dioxide production, and the energy and heat changes. The authors realised this and stated that their work and its discussion were only in the nature of a preliminary communication. A time came, however, in 1915 when the same authors, in giving the Croonian Lecture to the Royal Society, got the opportunity of discussing their results in the light of much further knowledge which had proceeded from research that their work had undoubtedly stimulated. They were prepared by this time to accept a wider framework in which to fit their lactic acid results—the Croonian Lecture, " The Respiratory Process in Muscle."

By this time also A. V. Hill and Parnas, working independently, had studied the wider problems of muscle metabolism raised by the Fletcher and Hopkins lactic acid work. They had investigated and attempted to correlate such things as heat production, oxygen uptake, and carbon dioxide formation, together with lactic acid production and disappearance under different conditions. In the Croonian Lecture, Fletcher and Hopkins took up all these new facts and discussed them in a masterly way. Their general conclusion was that lactic acid was a major factor in the wider problem of energy production in the body from carbohydrate and in the special case of muscular contraction. The emphasis they placed on lactic acid in muscular contraction can be seen from the following quotation:

> " In the evolution of muscle it would appear that advantage, so to speak, has been taken of this phase in carbohydrate degradation and that, by appropriate arrangement of the cell elements, the lactic acid before it leaves the tissue in its final combustion is assigned the particular position in which it can induce those tension changes upon which all the wonders of animal movement depend."

Since 1915 an enormous number of facts, especially on the chemical side, have been obtained as regards metabolic changes accompanying muscular contraction, but we still do not know the answer to many of the essential problems. In recent years interest in lactic acid has tended to diminish. This is due in part to the discovery that muscle can show contractions for a limited time even in presence of iodoacetic acid, a substance which inhibits one of the dehydrogenases necessary for glycolysis and therefore prevents lactic acid formation. Moreover the discovery of creatine phosphate and, more recently, of the adenosine triphosphate–actomyosin system, has focused attention on these as being the factors more closely linked with muscular activity. The breakdown of carbohydrate is, of course, still believed to be necessary to restore energy to the system—to rewind the mechanism as it were—but even here, pyruvic acid rather than lactic acid seems to be the primary product. It is held that lactic acid can arise by reduction from the pyruvic acid, but only to a significant extent when oxygen is excluded or, *in vivo*, when the muscle is working so strenuously that the blood-flow cannot supply enough oxygen to maintain fully aerobic conditions

Although lactic acid tends to be regarded as of secondary importance in muscular contraction, the work of Hopkins and others on this acid was at any rate an essential step leading to the more recent discoveries. Moreover, the general technique which Hopkins used in his experiments on muscle has been a model for many other workers, not least his insistence on isolating the substance under investigation as a pure, analysable specimen.

In consequence of the influence on his further work, it is important to observe that in 1915 Hopkins was still greatly interested in lactic acid oxidation and regarded this, from the point of view of production of energy in the body, as one of the major problems. It will be seen in a moment that he placed acetoacetic acid, one of the products of fat metabolism, in the same category as lactic acid as holding an important biological secret from the point of view of oxidative change and the supply of energy, and it was this combined interest in oxidation and in these small molecules that brought about his entry into the great field of tissue oxidations.

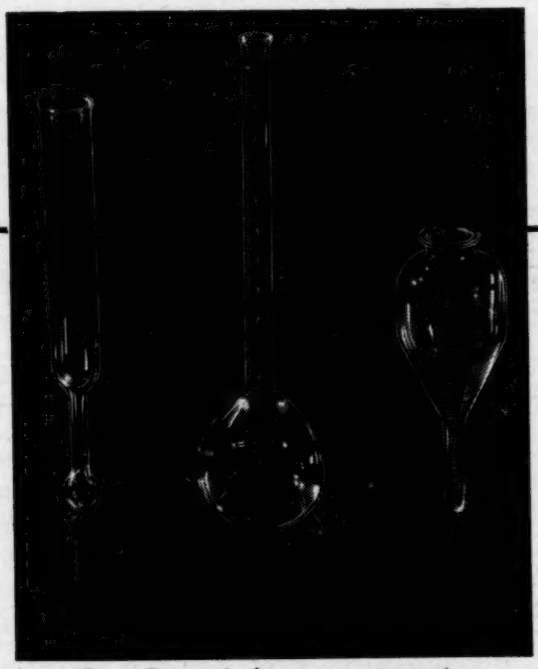
Hopkins has been greatly honoured for his work on vitamins, and it may be expected that this work will be discussed at length in this lecture. I do not, however, propose to spend much time on it, partly because the work is already so well known. It can be said at once that the scientific world was ripe for the leadership and direction given by the Hopkins publication in 1912 of " The Importance of Accessory Food Factors in Normal Dietaries." Hopkins himself often said to me in the years 1905—1907 that he thought the whole subject of nutrition was on the point of being revolutionised. Curiously enough, in spite of the lecture published in the *Analyst*

in 1906, which has become world-famous because in it he helped to foreshadow the importance of these accessory food factors, and, in spite of the fact that it was in this year that he published his work on the nutritional value of tryptophan, it never seemed to occur to him that these were the basis of the discoveries that were to revolutionise the science of nutrition; at least that is the impression left on my mind in looking back to those years. The fact is that this particular field of feeding young animals on synthetic diets of purified substances had been so long cultivated by previous workers, extending back to the work of Lunin in 1881, that a study of the literature leaves the actual new discoveries which were made by Hopkins in this work as less impressive than would be expected. It was rather his biological insight and his remarkable power of writing about the subject that impress all readers with the conviction that here we had at last a leader in physiological chemistry who had placed the subject in its proper, important perspective. In this work Hopkins's main facts were twofold: (1) That young rats on synthetic diets of purified substances consisting of protein, fat, carbohydrate, and salts will soon stop growing, but that if 2—3 c.c. of milk per rat per day are added to the diet growth will be resumed; if, on the other hand, young growing rats are on the diet plus the milk, and the milk is removed, then the rats soon stop growing. (2) That milk contains something which in minute quantities stimulates growth, and that this, in turn, causes an increase in appetite; on the contrary, cutting out the milk from the diet removed the growth stimulus, and cessation of growth then leads to a loss of appetite. It must be quite clear that, according to this work, it is not primarily the fact that the animals eat less that makes them grow less or that eating more makes them grow more, but the fact that the growth stimulus is present or absent and the appetite tends to adjust itself accordingly. There are times, it is pointed out, when the animals are eating much more than would be expected from their rate of growth and that on other occasions they are eating much less than would be expected. Another point emphasised is the quantitative aspect of the experiments.

The whole subject moved so rapidly from this time that little critical attention was paid to the detailed experimental facts as demonstrated by Hopkins. The growth curves that he showed in the publication were, however, reproduced in all parts of the world, but it is a matter of some interest to know that neither Hopkins himself nor anybody else was able to repeat the particular experiments—that is, the growth stimulus supplied by 2—3 c.c. of milk per rat per day. There was apparently some unknown condition in the experiments essential for their successful repetition (a state of affairs not uncommon in biological research). This fact, although of no real practical importance, because of the further development of the subject in America especially by Osborn and Mendel and also by MacCollum and his colleagues, greatly troubled Hopkins for many years, and it was only in 1945 that he returned to the subject and claimed to have found out the cause of the difficulty of repeating the early work. The secret apparently was that in the earlier work he used potato starch in his synthetic diet and this had led to a condition later known as refection. In refection, undigested starch grains collect in the cæcum and become a medium for growth of bacteria which produce water-soluble vitamins. It is possible under such conditions to get good growth in young rats without any additional vitamins. It was under such conditions that Hopkins was able to show the action of these small quantities of milk. The main point is that, in any case, this investigation of 1912 had a remarkable influence on research in this subject in all parts of the world.

Apart from the Croonian Lecture of 1915, there was an interval of nine years between the vitamin paper in 1912 and his next really important contribution on "An Autoxidisable Constituent of the Cell," published in 1921. The war was undoubtedly responsible for the interruption of Hopkins's research activities during this period, and from the point of view of scientific discovery this can only be regarded as a calamity. I wish, however, to call attention to his remarkable address in 1913 on "The Dynamic Side of Biochemistry," an address given as President of the Physiological Section to the British Association. Every biochemist or would-be biochemist ought to read this address.

By this time Hopkins had attained to his fullest stature as a biochemical philosopher, and it was his outlook on the chemical processes of living tissues which he then announced that bore such remarkable fruit in later years. I should like just to indicate some of the points of this discourse. In the first place he states his view that the raw material of metabolism is so prepared as to secure that it will be in the form of substances of small molecular weight. These views were of course much more striking then than they are now. Not only does he continue to discuss this point at length, but he deprecates the view of the physiologist that biological phenomena occur within a biogen or living molecule, or, in the case of muscle, inogen, where all directive power can be attributed in some vague sense to its quite special properties. Instead



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